

A Nonparametric Maximum Likelihood Approach for Partially Observed Cured Data with Left Truncation and Right-Censoring

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Abstract

Partially observed cured data occur in the analysis of spontaneous abortion (SAB) in observational studies in pregnancy. In contrast to the traditional cured data, such data has an observable ‘cured’ portion as women who do not abort spontaneously. The data is also subject to left truncate in addition to right-censoring because women may enter or withdraw from a study any time during their pregnancy. Left truncation in particular causes unique bias in the presence of a cured portion. In this paper, we study a cure rate model and develop a conditional nonparametric maximum likelihood approach. To tackle the computational challenge we adopt an EM algorithm making use of “ghost copies” of the data, and a closed form variance estimator is derived. Under suitable assumptions, we prove the consistency of the resulting estimator involving an unbounded cumulative baseline hazard function, as well as the asymptotic normality. Simulation results are carried out to evaluate the finite sample performance. We present the analysis of the motivating SAB study to illustrate the power of our model addressing both occurrence and timing of SAB, as compared to existing approaches in practice.

Keywords: Cure rate model, EM algorithm, ghost copy, left truncation, NPMLE, observable Cure.

1 Introduction

Our work was motivated by research carried out at the Organization of Teratology Information Specialists (OTIS), which is a North American network of university or hospital based teratology services that counsel between 70,000 and 100,000 pregnant women every year. Research subjects are enrolled from the Teratology Information Services and through other methods of recruitment, where the mothers and their babies are followed over time. Phone interviews are conducted through the length of the pregnancy along with pregnancy diaries recorded by the mother. An outcome phone interview is conducted shortly after the pregnancy ends, and if it results in a live birth, a dysmorphology exam is done within six months and with further follow-ups at one year and possibly later dates. Recently it has been of interest to assess the effects of medication exposures on spontaneous abortion (SAB) (Xu and Chambers, 2011; Chambers *et al.*, 2011). Here we examine the OTIS autoimmune disease in pregnancy database for risk factors as well as effects of medications on spontaneous abortion.

By definition SAB occurs within the first 20 weeks of gestation; any spontaneous pregnancy loss after that is called still birth. Ultimately we would like to know if an exposure modifies the risk of SAB for a woman, which may be increased or decreased. It is known that in the population for clinically recognized pregnancies the rate of SAB is about 12% (Wilcox *et al.*, 1988). On the other hand, in our database the empirical SAB rate is consistently lower than 10%. This is due to the fact that women may enter a study any time before 20 weeks' gestation. Figure 1 left panel shows the histograms of study entry times up to 20 weeks of gestation from our autoimmune disease in pregnancy database. This way women who have early SAB events are less likely to be captured in our studies, and such selection bias is known as left truncation in survival analysis. Left truncation has been studied by many authors since the 1980s, and has attracted much recent attention in the context of length-biased data (Asgharian *et al.*, 2006; Qin *et al.*, 2011, among others). Figure 1 right panel shows the left truncated

Kaplan-Meier curve for the SAB event.

As seen from the Kaplan-Meier curve the majority of the pregnant women are free of SAB; they are considered ‘cured’ in the time-to-event context. Cure rate models are well studied in the literature for right-censored data. The models effectively analyze the survival distribution of those who are susceptible along with the probability of an individual being ‘cured’. In the approaches using mixture models, logistic regression is often used to model the cured probability. For the dependency of the survival function on the covariates among the non-cured, various regression models have been considered: the Cox proportional hazards model (Kuk and Chen, 1992; Sy and Taylor, 2000), transformation models (Lu and Ying, 2004), and richly parametrized models when the shape of the hazard function is of interest (Hanson *et al.*, 2003). Cure rate models have also been developed along the lines of non-mixture models (Chen *et al.*, 1999; Zeng *et al.*, 2006). In addition to right-censored data, cure-rate models have also been developed for interval-censored data (Kim and Jhun, 2008). To our best knowledge, however, they have not been considered for truncated data which, unlike censoring, poses a unique set of challenges. While left truncation has been well studied in the literature, the challenges are again unique in the presence of a cured portion. Most importantly, left truncation leads to selection bias that needs to be explicitly counted for, and in the process of doing so computational challenges also arise, as will be seen below.

Cure models are used in various biomedical studies where data often include a substantial portion of ‘long-term’ survivors who are no longer susceptible to the event of interest (Farewell, 1982, 1986). Our data however, differs from classical cured data where the ‘long-term’ survivors are never observed to be cured, rather they are censored at a finite time point (Sy and Taylor, 2000; Lu and Ying, 2004, often taken as the maximum). In our case, ‘cured’ is defined as surviving 20 weeks of gestation, and we observe over 80% of our subjects as cured from SAB.

In the following we consider the mixture cure rate model. This choice has been made based on in-depth discussions with our scientific collaborators, because it is important to understand both the risk factors for SAB (yes/no) as well as the predictors of timing of SAB events among those who experience them. Different timing of SAB can reflect different underlying biological processes. In the next section we show that with many observed ‘cured’ women in our data, a slightly different likelihood than the one commonly seen in the literature should be used. We discuss computational challenges with the likelihood, and adopt an EM algorithm using ‘ghost copies’ of the observed data. In section 3, the resulting estimator is shown to be consistent and asymptotic normal, despite the fact that the cumulative baseline hazard function diverges at the finite time point before ‘cure’ is achieved. We illustrate the effectiveness of the method on finite samples via simulation experiments in section 4. We conclude with the analysis of SAB data from the OTIS database described above.

2 Model and NPMLE

2.1 Model and partially observed cured data

Let $\tau < \infty$ be a strict upper bound of time for the event of interest, beyond which a subject is considered cured. In the pregnancy example above, this would be the 20 weeks of gestation. The whole population consists of two subpopulations: cured and non-cured. Let the binary random variable A indicate whether a subject belongs to the non-cured subpopulation; and let $T^* \in (0, \tau)$ be the failure time random variable for this subpopulation. The overall outcome time T is given by the mixture (Lu and Ying, 2004): $T = AT^* + (1 - A)\tau$. Let \mathbf{Z}_1 and \mathbf{Z}_2 be two covariate vectors; they may share common covariates depending on the application. We assume that A given \mathbf{Z}_1 follows the logistic regression model

$$P(A = 1|\mathbf{Z}_1, \mathbf{Z}_2) = p = \frac{e^{\boldsymbol{\alpha}^\top \mathbf{Z}_1}}{1 + e^{\boldsymbol{\alpha}^\top \mathbf{Z}_1}},$$

and that T^* given \mathbf{Z}_2 follows the proportional hazard regression model with cumulative baseline hazard function $\lambda_0(t) = \int_0^t \lambda_0(u)du$:

$$P(T^* \geq t | \mathbf{Z}_2) = S(t | \mathbf{Z}_2) = \exp\{-\Lambda_0(t)e^{\beta^\top \mathbf{Z}_2}\}.$$

Note that $\Lambda_0(\tau) = +\infty$ so that $S(\tau | \mathbf{Z}_2) = 0$.

Our data is subject to left truncation and right-censoring. Let Q be the left truncation time and C the right-censoring time, satisfying $0 \leq Q < C$; we also assume that they are independent of (A, T^*) conditioning on \mathbf{Z}_1 and \mathbf{Z}_2 . For subjects $i = 1, \dots, n$, the observed data include \mathbf{Z}_{1i} , \mathbf{Z}_{2i} , Q_i , $X_i = T_i \wedge C_i$, $\delta_i^1 = A_i \cdot I(T_i \leq C_i)$, $\delta_i^0 = (1 - A_i)I(C_i \geq \tau)$ and $\delta_i^c = I(C_i < T_i \leq \tau)$. In other words δ_i^1 is the indicator that a subject has an observed event (non-cured), δ_i^0 is the indicator that a subject is observed to be cured, and δ_i^c is the indicator that a subject is censored before τ so that we do not know whether she is cured or not. Note that the subject i is observed only if $T_i > Q_i$, hence left truncation is known to lead to a biased sample from the population. We note again that our data is different from the classical cure model literature, where the cured individuals are always treated as censored; we refer to our data as *partially observed cured data*. Because of right-censoring, A_i may not be observed; but we emphasize here that we do observe many $A_i = 0$ in our data.

Denote $\theta = (\alpha, \beta, \Lambda_0)$. For the purposes of nonparametric maximum likelihood estimation (NPMLE), it is necessary to discretize Λ_0 to be $\Lambda_0(t) = \sum_{k=1}^K \lambda_k I(t \geq t_k)$, where $0 < t_1 < \dots < t_K < \infty$ are the unique failure times (Johansen, 1983; Murphy, 1994). We apply the likelihood approach conditional upon the left truncation time Q_i and the right-censoring time C_i , as no parametric distributional assumptions are made about these two random variables. Denote $p_i = e^{\alpha^\top \mathbf{Z}_{1i}} / (1 + e^{\alpha^\top \mathbf{Z}_{1i}})$, $\lambda_i(t) = \lambda_0(t) \exp(\beta^\top \mathbf{Z}_{2i})$, $f_i(t) = \lambda_i(t)S_i(t)$, and $S_i(t) = \exp\{-\Lambda_0(t)e^{\beta^\top \mathbf{Z}_{2i}}\}$. The likelihood

for our observed data is

$$\begin{aligned}
L(\boldsymbol{\theta}) &= \prod_{i=1}^n L_i(\boldsymbol{\theta}; X_i, \delta_i^1, \delta_i^0, \delta_i^c | T_i > Q_i, \mathbf{Z}_{1i}, \mathbf{Z}_{2i}, Q_i, C_i) \\
&= \prod_{i=1}^n \frac{\{p_i \lambda_i(X_i) S_i(X_i)\}^{\delta_i^1} (1 - p_i)^{\delta_i^0} \{1 - p_i + p_i S_i(X_i)\}^{\delta_i^c}}{1 - p_i + p_i S_i(Q_i)}, \tag{1}
\end{aligned}$$

where $1 - p_i + p_i S_i(X_i) = P(T_i > Q_i)$.

2.2 NPMLE through EM

Complete data likelihood

The complexity of observed likelihood (1) leads to the challenge of optimization. To reduce the problem we follow the approach of Vardi (1985), rediscovered recently by Qin *et al.* (2011).

To augment the observed data, we first note that the group indicator A_i is latent whenever censoring occurs. In addition, we compensate for the left truncation through the “ghost copy” algorithm proposed in Qin *et al.* (2011). For each observed subject with the pair of covariates $(\mathbf{Z}_{1i}, \mathbf{Z}_{2i})$ and entry time Q_i , there are M_i hypothetical “truncated samples” with latent event time $\tilde{T}_{ij} < Q_i$, $j = 1, \dots, M_i$. The resulting complete likelihood is

$$\begin{aligned}
L^c(\boldsymbol{\theta}) &= \prod_{i=1}^n \{p_i \lambda_i(X_i) S_i(X_i)\}^{\delta_i^1} (1 - p_i)^{\delta_i^0} \{p_i S_i(X_i)\}^{A_i \delta_i^c} (1 - p_i)^{(1 - A_i) \delta_i^c} \\
&\quad \times p_i^{M_i} \prod_{j=1}^{M_i} \prod_{k: t_k \leq Q_i} \{\lambda_k e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} S_i(t_k)\}^{I(\tilde{T}_{ij} = t_k)} \tag{2}
\end{aligned}$$

In this way, the two sets of parameters $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$ are separated in the complete data likelihood. All remaining product terms are those in the usual likelihoods for the logistic and the Cox regression model. Consequently, the M-step update is instantly available from existing solvers.

Given the observed data \mathcal{O} , it can be seen that for subject i who is censored at X_i , the unobserved group indicator A_i follows Bernoulli distribution with $P(A_i = 1) =$

$p_i S_i(X_i) / \{1 - p_i + p_i S_i(X_i)\}$. For a subject with truncation time Q_i and covariates $(\mathbf{Z}_{1i}, \mathbf{Z}_{2i})$, it can be seen that the number of truncated “ghost” copies M_i follows the geometric distribution with probability $P(T_i < Q_i) = p_i \{1 - S_i(Q_i)\}$. For the “ghost” event times let \tilde{T}_{ij} be one of the observed event times $t_k < Q_i$ with probability proportional to $f_i(t_k) = \lambda_k e^{\beta^\top \mathbf{Z}_{2i}} S_i(t_k)$:

$$P(\tilde{T}_{ij} = t_k | M_i, \mathcal{O}) = \frac{I(t_k \leq Q_i) \lambda_k e^{\beta^\top \mathbf{Z}_{2i}} S_i(t_k)}{\sum_{k: t_k \leq Q_i} \lambda_k e^{\beta^\top \mathbf{Z}_{2i}} S_i(t_k)}. \quad (3)$$

By restricting the “ghost” event times to the observed event times, we are able to exploit the convenience of directly applying the weighted Cox regression later. The price we pay is a slight discrepancy between $\sum_{k: t_k \leq Q_i} \lambda_k e^{\beta^\top \mathbf{Z}_{2i}} S_i(t_k)$ and $1 - S_i(Q_i)$. Integrating out the latent variables in $L^c(\boldsymbol{\theta})$ does not give exactly the observed likelihood $L(\boldsymbol{\theta})$. However, we show later that this difference is asymptotically negligible so that the solution from the above EM is asymptotically equivalent to the true NPMLE.

The EM Algorithm

From (2) we can write the complete data log-likelihood $l^c = \log L^c$ as

$$l^c(\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\lambda}) = \sum_{i=1}^n \left[\delta_i^1 A_i \sum_{k=1}^K I\{X_i = t_k\} \log f_i(t_k) + M_i \sum_{k: t_k < Q_i} I\{\tilde{T}_i = t_k\} \log f_i(t_k) \right. \\ \left. + (1 - \delta_i^1) A_i \log S_i(X_i) + (1 - A_i) \log(1 - p_i) + (A_i + M_i) \log(p_i) \right], \quad (4)$$

where $\boldsymbol{\lambda} = (\lambda_1, \dots, \lambda_K)$.

Though the algorithm runs stably from any initial values of the parameters in the support, we recommend to fit a naïve logistic regression without censored subjects for $\boldsymbol{\alpha}^{(0)}$ and a naïve Cox regression for $\boldsymbol{\beta}^{(0)}$ and $\boldsymbol{\lambda}^{(0)}$ treating the observed cured subjects as censored at τ , to minimize the number of iterations until convergence.

E-step

At the $(l + 1)$ -th iteration ($l = 0, 1, \dots$), let $\boldsymbol{\alpha}^{(l)}, \boldsymbol{\beta}^{(l)}, \boldsymbol{\lambda}^{(l)}$ be the parameter values at the current iteration upon which $p_i^{(l)}, f_i^{(l)}$ and $S_i^{(l)}$ are defined. The distributions

of the latent variables conditioning on the observed data are given in the above, and their conditional expectations can be computed as

$$E[I\{\tilde{T}_{ij} = t_k\} | M_i, \mathcal{O}; \boldsymbol{\alpha}^{(l)}, \boldsymbol{\beta}^{(l)}, \boldsymbol{\lambda}^{(l)}] = \frac{I(t_k < Q_i) f_i^{(l)}(t_k)}{\sum_{h: t_h < Q_i} f_i^{(l)}(t_h)}, \quad (5)$$

$$E[M_i | \mathcal{O}; \boldsymbol{\alpha}^{(l)}, \boldsymbol{\beta}^{(l)}, \boldsymbol{\lambda}^{(l)}] = \frac{p_i^{(l)} \sum_{k: t_k < Q_i} f_i^{(l)}(t_k)}{1 - p_i^{(l)} \sum_{k: t_k < Q_i} f_i^{(l)}(t_k)}, \quad (6)$$

$$E[A_i | \mathcal{O}; \boldsymbol{\alpha}^{(l)}, \boldsymbol{\beta}^{(l)}, \boldsymbol{\lambda}^{(l)}] = \delta_i^1 + \delta_i^c \frac{p_i^{(l)} S_i^{(l)}(X_i)}{1 - p_i^{(l)} + p_i^{(l)} S_i^{(l)}(X_i)}. \quad (7)$$

Since the latent variables all enter linearly into the complete data log-likelihood, the expected complete data log-likelihood is

$$E(l^c | \mathcal{O}) = \sum_{i=1}^n \sum_{k=1}^K \left\{ w_{i,k}^f \log f_i(t_k) + w_i^S \log S_i(X_i) + w_{0,i}^p \log(1 - p_i) + w_{1,i}^p \log(p_i) \right\}, \quad (8)$$

where the weights are computed as

$$\begin{aligned} w_{i,k}^f &= \delta_i^1 I\{X_i = t_k\} + \frac{p_i^{(l)} f_i^{(l)}(t_k)}{1 - p_i^{(l)} \sum_{h: t_h < Q_i} f_i^{(l)}(t_h)} I\{t_k < Q_i\}, \\ w_i^S &= \delta_i^c \frac{p_i^{(l)} S_i^{(l)}(X_i)}{1 - p_i^{(l)} + p_i^{(l)} S_i^{(l)}(X_i)}, \\ w_{0,i}^p &= \delta_i^0 + \delta_i^c \frac{1 - p_i^{(l)}}{1 - p_i^{(l)} + p_i^{(l)} S_i^{(l)}(X_i)}, \\ w_{1,i}^p &= \delta_i^1 A_i + \delta_i^c \frac{p_i^{(l)} S_i^{(l)}(X_i)}{1 - p_i^{(l)} + p_i^{(l)} S_i^{(l)}(X_i)} + \frac{p_i^{(l)} \sum_{k: t_k < Q_i} f_i^{(l)}(t_k)}{1 - p_i^{(l)} \sum_{k: t_k < Q_i} f_i^{(l)}(t_k)}. \end{aligned}$$

M-step

From (8) the expected log-likelihood can be written as the sum of two parts, so that the M-step can be achieved using a weighted logistic regression optimized over $\boldsymbol{\alpha}$:

$$l_{glm} = \sum_{i=1}^n w_{0,i}^p \log(1 - p_i) + w_{1,i}^p \log(p_i);$$

and a weighted Cox proportional hazard regression optimized over $\boldsymbol{\beta}$:

$$l_{coxph} = \sum_{i=1}^n \sum_{k=1}^K w_{i,k}^f \log f_i(t_k) + \sum_{i=1}^n w_i^S \log S_i(X_i).$$

Easily implemented solution is available from existing *glm* and *coxph* solvers in R, to obtain $\boldsymbol{\alpha}^{(l+1)}$, $\boldsymbol{\beta}^{(l+1)}$ and $\boldsymbol{\lambda}^{(l+1)}$.

Variance Estimator

At convergence of the EM algorithm where $\hat{\boldsymbol{\theta}}$ denotes the NPMLE, the Louis (1982) formula can be used to give the observed Fisher information:

$$I_{obs}(\hat{\boldsymbol{\theta}}) = \sum_{i=1}^n E_{\hat{\boldsymbol{\theta}}}[B_i|\mathcal{O}] - \sum_{i=1}^n E_{\hat{\boldsymbol{\theta}}}[\mathbf{S}_i \mathbf{S}_i^\top |\mathcal{O}] - 2 \sum_{i < i'}^n E_{\hat{\boldsymbol{\theta}}}[\mathbf{S}_i|\mathcal{O}] E_{\hat{\boldsymbol{\theta}}}[\mathbf{S}_{i'}|\mathcal{O}]^\top, \quad (9)$$

where \mathbf{S}_i and B_i are the gradient ∇l_i^c and the negatives of Hessian $-\nabla^2 l_i^c$ of the complete data log-likelihood. The above is in closed form, and the details are given in Appendix B. We show in the next section that (9) provides a consistent variance estimator for the NPMLE, and its use in association with the NPMLE has been advocated in the literature (Vaida and Xu, 2000; Zeng and Lin, 2007; Gamst *et al.*, 2009).

3 Theory

Let $\boldsymbol{\theta}_0 = (\boldsymbol{\alpha}_0, \boldsymbol{\beta}_0, \Lambda_0(\cdot))$ denote the true parameter value. Following Andersen *et al.* (1993), we define the counting process $N_i(t) = \delta_i^1 I(X_i \leq t)$ and the at-risk process $Y_i(t) = I(Q_i \leq t \leq X_i)$. Their sums are denoted as $\bar{N}(t) = \sum_{i=1}^n N_i(t)$, and $\bar{Y}(t) = \sum_{i=1}^n Y_i(t)$. By Doob-Meyer decomposition, a martingale with respect to the filtration $\mathcal{F}_t = \sigma\{N_i(u), Y_i(u), \mathbf{Z}_1, \mathbf{Z}_2, u \leq t\}$ is

$$M_i(t) = N_i(t) - \int_0^t \phi_i^{\boldsymbol{\theta}_0}(u) Y_i(u) e^{\boldsymbol{\beta}_0^\top \mathbf{Z}_{2i}} d\Lambda_0(u), \quad (10)$$

where

$$\phi_i^{\boldsymbol{\theta}}(t) = \frac{\exp\{\boldsymbol{\alpha}^\top \mathbf{Z}_{1i} - \Lambda(t) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}}\}}{1 + \exp\{\boldsymbol{\alpha}^\top \mathbf{Z}_{1i} - \Lambda(t) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}}\}} = P_{\boldsymbol{\theta}}(A_i = 1 | X_i \geq t). \quad (11)$$

To make use of the martingale framework, we write the observed log-likelihood $l_n = \log L$, where $L(\boldsymbol{\theta})$ was given in (1), as

$$\begin{aligned} l_n = & \sum_{i=1}^n \int_0^\tau \log \left(\phi_i^{\boldsymbol{\theta}}(u) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right) dN_i(u) - \int_0^\tau Y_i(u) \phi_i^{\boldsymbol{\theta}}(u) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} d\Lambda(u) \\ & + \int_0^\tau \log \left(\Delta\Lambda(u) \right) dN_i(u), \end{aligned}$$

where $\Delta\Lambda(u)$ is the size of jump of the baseline cumulative hazard at u (Murphy, 1994). We establish the theory under the following assumptions. The vector norm throughout this paper is the uniform norm, i.e. the largest absolute value among all elements.

Assumption 1. *The true finite-dimensional parameter (α_0, β_0) is an element of the interior of a compact set $\{(\alpha, \beta) : \|\alpha\| \vee \|\beta\| \leq D_1\}$ for some constant D_1 .*

Assumption 2. *The covariates $(\mathbf{Z}_1, \mathbf{Z}_2)$ follow distribution $F_Z(\cdot, \cdot)$. They are bounded a.s.: there exists $D_2 > 0$, such that $P(\max\{\|\mathbf{Z}_1\|, \|\mathbf{Z}_2\|\} \leq D_2) = 1$. Also, their covariance matrices $\text{Var}(\mathbf{Z}_1)$ (without intercept term) and $\text{Var}(\mathbf{Z}_2)$ are both positive-definite. Denote constant m such that*

$$0 < m^{-1} = e^{-D_1 D_2} \leq e^{\alpha^\top \mathbf{Z}_1} \wedge e^{\beta^\top \mathbf{Z}_2} \leq e^{\alpha^\top \mathbf{Z}_1} \vee e^{\beta^\top \mathbf{Z}_2} \leq e^{D_1 D_2} = m < \infty \quad \text{a.s..} \quad (12)$$

Assumption 3. *The baseline cumulative hazard function $\Lambda_0(t)$ is a non-decreasing continuous function on $[0, \tau)$. $\Lambda_0(0) = 0$ and $\Lambda_0(\tau-) = \infty$. And*

$$\inf_{t \in [0, \tau]} E[Y(t) | \mathbf{Z}_1, \mathbf{Z}_2] > \varepsilon > 0, \quad \text{a.s..} \quad (13)$$

Assumption 4. *There exists $\zeta \in (0, \tau)$ such that $P(Q > \zeta) = 0$. $\Lambda_0(t)$ is strictly increasing over $[0, \zeta]$, and $E[Y(t) | \mathbf{Z}_1, \mathbf{Z}_2]$ is Lipschitz continuous w.r.t to $\Lambda_0(t)$ on $[0, \zeta]$ a.s.; that is, there is a constant*

$$\mathcal{L} \geq \sup_{0 \leq t < s \leq \zeta} \left\{ \frac{|E[Y(t) | \mathbf{Z}_1, \mathbf{Z}_2] - E[Y(s) | \mathbf{Z}_1, \mathbf{Z}_2]|}{|\Lambda_0(t) - \Lambda_0(s)|} \right\}, \quad \text{a.s..} \quad (14)$$

The above Assumption 3 is specifically made for cure rate models with an observable cured portion. This assumption enforces that the failure time must occur prior to a well-defined upper bound. Equation (13) requires that certain proportion of subjects enter the study at time zero. While this may not always be the case for our pregnancy studies, time zero may be replaced by the earliest entry time into the study and the inference is conditional upon survival beyond that time, and all the results established in this section carry over. Assumption 4 gives the regularity conditions on truncation

and censoring. The truncation times should be bounded away from time τ ; this is required in order to establish Lemma 1 below. The truncation-censoring distribution also has to possess certain level of continuity with respect to the distribution of event time. For example, the continuity condition is satisfied when the distributions for Q , C and T given \mathbf{Z}_1 and \mathbf{Z}_2 all have densities that are bounded away from ∞ and 0 almost surely. This condition can be weakened to allow $\Lambda_0(t)$ to be constant over some open set and require only that $E[Y(t)|\mathbf{Z}_1, \mathbf{Z}_2]$ is Lipschitz continuous with respect to $\Lambda_0(t)$ on a open set $\Omega \subset [0, \zeta]$ consisting of finite many open intervals, on which $\int_{\Omega} d\Lambda_0 = \Lambda_0(\zeta)$. All theoretical results under this weakened condition can be achieved by repeatedly applying the steps in the current proof.

For the asymptotic normality we make the following assumption where τ' is defined later.

Assumption 3'. *The baseline cumulative hazard $\Lambda_0(t)$ is a non-decreasing continuous function on $[0, \tau']$. $\Lambda_0(0) = 0$, $\Lambda_0(\tau') < \infty$ and $\Lambda_0(\tau-) = \infty$. And*

$$\inf_{t \in [0, \tau']} E[Y(t)|\mathbf{Z}_1, \mathbf{Z}_2] > \varepsilon > 0, \quad a.s..$$

3.1 Existence of NPMLE

First, we show the existence of the NPMLE.

Theorem 1. *Under Assumptions 1 and 2, if $\sum_{i=1}^n N_i(\tau) > 0$, then a maximizer of $l_n(\boldsymbol{\theta})$, $\hat{\boldsymbol{\theta}} = (\hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\beta}}, \hat{\Lambda}(\cdot))$ exists and is finite.*

For the proof we use the same technique as in Murphy (1994). All the proofs are in Appendix A.

We now show that the solution from the previously described EM algorithm is asymptotically equivalent to the NPMLE.

Lemma 1. *Let $\tilde{\boldsymbol{\theta}}$ be the solution from the EM algorithm with complete data likelihood (2) and $\hat{\boldsymbol{\theta}}$ be the NPMLE for the observed likelihood (1). Under Assumptions 1 - 4,*

$$n^{-1}\{l_n(\hat{\boldsymbol{\theta}}) - l_n(\tilde{\boldsymbol{\theta}})\} = O_p(1/n).$$

Theorem 2. *Under Assumptions 1- 4, $\|\hat{\boldsymbol{\theta}} - \tilde{\boldsymbol{\theta}}\| = o_p(1)$.*

Theorem 2'. *Under Assumptions 1, 2, 4 and 3', $\hat{\boldsymbol{\theta}} - \tilde{\boldsymbol{\theta}} = o_p(1/\sqrt{n})$.*

3.2 Consistency of NPMLE

Next, we show the consistency of the NPMLE.

Theorem 3. *Under Assumptions 1 - 4, the NPMLE estimator for L in (1), $\hat{\boldsymbol{\theta}} = (\hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\beta}}, \hat{\Lambda}(\cdot))$, is consistent. That is*

$$\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha}_0 \rightarrow 0, \quad \hat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0 \rightarrow 0, \quad \sup_{t \in [0, \tau]} |e^{-\hat{\Lambda}(t)} - e^{-\Lambda_0(t)}| \rightarrow 0 \quad a.s..$$

The proof follows the general framework in Murphy (1994). The estimator for the baseline hazard satisfies the equation

$$\hat{\Lambda}(t) = \int_0^t \left\{ \sum_{i=1}^n W_i^{\hat{\boldsymbol{\theta}}}(u) e^{\hat{\boldsymbol{\beta}}^\top \mathbf{Z}_{2i}} \right\}^{-1} d\bar{N}(u), \quad (15)$$

where

$$W_i^{\boldsymbol{\theta}}(t) = \{\delta_i^1 + \delta_i^c \phi_i^{\boldsymbol{\theta}}(X_i)\} I\{t \leq X_i\} - \phi_i^{\boldsymbol{\theta}}(Q_i) I\{t \leq Q_i\}, \quad (16)$$

and $\phi_i^{\boldsymbol{\theta}}(\cdot)$ is given in (11). A bridge between $\hat{\Lambda}$ and Λ_0 is constructed as

$$\bar{\Lambda}(t) = \int_0^t \left\{ \sum_{i=1}^n \phi_i^{\boldsymbol{\theta}_0}(u) Y_i(u) e^{\boldsymbol{\beta}_0^\top \mathbf{Z}_{2i}} \right\}^{-1} d\bar{N}(u). \quad (17)$$

The details of the proof deserve some extra comments here, as it achieves the a.s. convergence with a baseline hazard unbounded in its support using a few innovative steps. First, we apply Helly's selection theorem to the Càdlàg function sequence $e^{-\hat{\Lambda}}$. Then, the upper bound for $\hat{\Lambda}$ in any interval $[0, \tau^*] \subset (0, \tau)$ is established via the lower bound for $n^{-1} \sum_{i=1}^n W_i^{\hat{\boldsymbol{\theta}}}(u) e^{\hat{\boldsymbol{\beta}}^\top \mathbf{Z}_{2i}}$. We manage to show that the ratio $\gamma(t) = d\hat{\Lambda}(t)/d\bar{\Lambda}(t)$ is bounded between zero and infinity for all $t \in (0, \tau)$ despite the indefinite quotient at 0 and τ . Finally, we conclude the proof by showing that $\gamma(t) = 1$ using an identifiability argument.

For the purposes of the asymptotic normality below, we have a similar result:

Theorem 3'. *Under Assumptions 1, 2, 3' and 4, the NPMLE estimator for L^I defined later in (19), $\hat{\boldsymbol{\theta}} = (\hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\beta}}, \hat{\Lambda}(\cdot))$, is consistent. That is*

$$\hat{\boldsymbol{\alpha}} - \boldsymbol{\alpha}_0 \rightarrow 0, \quad \hat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0 \rightarrow 0, \quad \sup_{t \in [0, \tau']} |\hat{\Lambda}(t) - \Lambda_0(t)| \rightarrow 0 \quad a.s.. \quad (18)$$

3.3 Asymptotic Normality of NPMLE

The divergence of the cumulative baseline hazard Λ_0 at τ eventually becomes an obstacle in the study of weak convergence. It is involved in all the second order terms including both the parametric parts and the nonparametric part. Existing techniques, mostly relying on a finite upper bound of Λ_0 , cannot deal with it. To proceed with the theoretical endeavor, we avoid the divergent tail by slightly modifying the likelihood. That is, we make an interval censoring window (τ', τ) close to the end of study, so that the failure indicator A is always observed for those at-risk at time τ' , but their failure times are unknown if $A = 1$. We note that this is for technical reason only, so that the baseline cumulative hazard is always bounded at the observed failure times as $n \rightarrow \infty$. In practical applications this modification of the likelihood is unnecessary since the observed SAB events are recorded in dates, so that there is always at least one day gap between when a (possibly censored) SAB event can happen and when a woman is considered cured.

Let $\delta^\tau = A \cdot I(X > \tau')$ be the interval-censoring indicator in (τ', τ) . Notice that $S(t) - S(\tau) = S(t)$ for any $t < \tau$. We have the resulting interval-censored data likelihood that is modified from (1):

$$L^I(\boldsymbol{\theta}) = \prod_{i=1}^n \frac{\{p\lambda_i(X_i)e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}}S_i(X_i)\}^{\delta_i^1} (1-p_i)^{\delta_i^0} \{1-p_i+p_iS_i(X_i)\}^{\delta_i^c} \{p_iS_i(\tau')\}^{\delta_i^\tau}}{1-p_i+p_iS_i(Q_i)}. \quad (19)$$

The corresponding log-likelihood $l_n^I = \log L^I$ is

$$\begin{aligned} l_n^I = \sum_{i=1}^n \int_0^{\tau'} \log \left(\phi_i^\theta(u) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \triangle \Lambda(u) \right) dN_i(u) - \int_0^{\tau'} Y_i(u) \phi_i^\theta(u) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} d\Lambda(u) \\ + \{N_i(\tau) - N_i(\tau')\} \log \phi_i^\theta(\tau') + Y_i(\tau) \log(1 - \phi_i^\theta(\tau')). \end{aligned} \quad (20)$$

The proof then follows the framework in Murphy (1995) to verify the conditions of Theorem 3.3.1 from Van der Vaart and Wellner (1996). We shall describe the functional space in which weak convergence is established. Let H_∞ be the space containing elements in the form of $\mathbf{h} = (\mathbf{a}, \mathbf{b}, \eta)$, where the vectors \mathbf{a} and \mathbf{b} are of the same dimensions as $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$, respectively, and the function $\eta(\cdot)$ is defined on $[0, \tau']$ with $\eta(0) = 0$ and is of bounded variation, i.e. the total variation of η over $[0, \tau']$,

$$V_0^{\tau'} \eta = \sup_{\substack{0=u_0 < \dots < u_s = \tau' \\ s=1,2,\dots}} \sum_{j=1}^s |\eta(u_j) - \eta(u_{j-1})|$$

is finite. Define a norm $\|\cdot\|_H$ on H_∞ :

$$\|(\mathbf{a}, \mathbf{b}, \eta)\|_H = \|\mathbf{a}\|_1 + \|\mathbf{b}\|_1 + V_0^{\tau'} |\eta|,$$

and spaces indexed by a positive real number p

$$H_p = \{\mathbf{h} : \|\mathbf{h}\|_H < p\}.$$

For each p , define $l^\infty(H_p)$ as the functional space of all uniformly bounded linear map $H_p \mapsto \mathbb{R}$, i.e.

$$\forall \Psi \in l^\infty(H_p), \sup_{\mathbf{h} \in H_p} |\Psi(\mathbf{h})| < \infty.$$

The parameter $\boldsymbol{\theta} = (\boldsymbol{\alpha}, \boldsymbol{\beta}, \Lambda)$ as a function in $l^\infty(H_p)$ is defined as

$$\boldsymbol{\theta}(\mathbf{h}) = \mathbf{a}^\top \boldsymbol{\alpha} + \mathbf{b}^\top \boldsymbol{\beta} + \int_0^{\tau'} \eta(u) d\Lambda(u).$$

The induced functional norm is equivalent to the norm in (18) where consistency (Theorem 3') is established; we denote $\|\boldsymbol{\theta}\|$.

Theorem 4. *Let $\hat{\boldsymbol{\theta}} = (\hat{\boldsymbol{\alpha}}, \hat{\boldsymbol{\beta}}, \hat{\Lambda}_0(\cdot))$ be the NPMLE for the log-likelihood l_n^I in (20). Under Assumptions 1, 2, 3' and 4,*

$$\sqrt{n}(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}_0) \longrightarrow \mathcal{G}, \text{ in } l^\infty(H_p)$$

weakly for a tight Gaussian process \mathcal{G} on $l^\infty(H_p)$ with covariance process

$$\text{Cov}(\mathcal{G}(\mathbf{h}), \mathcal{G}(\mathbf{h}^*)) = \mathbf{a}^\top \boldsymbol{\sigma}_a^{-1}(\mathbf{h}^*) + \mathbf{b}^\top \boldsymbol{\sigma}_b^{-1}(\mathbf{h}^*) + \int_0^{\tau'} \eta(u) \sigma_\eta^{-1}(\mathbf{h}^*)(u) d\Lambda_0(u),$$

where $\mathbf{h} = (\mathbf{a}, \mathbf{b}, \eta)$, and $\sigma(\mathbf{h}) = (\boldsymbol{\sigma}_a(\mathbf{h}), \boldsymbol{\sigma}_b(\mathbf{h}), \sigma_\eta(\mathbf{h}))$ is given in the Appendix (A22).

Let $\hat{\sigma}$ be a nature estimator for the operator σ by substituting the true parameter θ_0 and expectation with the estimator $\hat{\theta}$ and the sample average.

Theorem 5. *Under Assumptions 1, 2, 3' and 4, $\hat{\sigma}$ is asymptotically equivalent to the information matrix in (9). The solution to $\mathbf{g} = \hat{\sigma}^{-1}(\mathbf{h})$ exists with probability going to 1 as n increases and*

$$\mathbf{a}^\top \hat{\sigma}_a^{-1}(\mathbf{h}^*) + \mathbf{b}^\top \hat{\sigma}_b^{-1}(\mathbf{h}^*) + \int_0^{\tau'} \eta(u) \hat{\sigma}_\eta^{-1}(\mathbf{h}^*)(u) d\hat{\Lambda}(u) \xrightarrow{P} \text{Cov}(\mathcal{G}(\mathbf{h}), \mathcal{G}(\mathbf{h}^*)).$$

4 Simulation study

4.1 Simulation setup

Here we detail our data simulation procedure for all of the simulation studies. Simulating cure-rate model data presents its own challenges. To be comparable with the spontaneous abortion data which we examine in the next section, we consider finite time τ , which is set to be 20 (weeks). The covariates are the same for the logistic and the Cox part of the regression models and, unless otherwise specified, consisting of $Z_1 \sim N(4, 1)$, with corresponding parameters (α_1, β_1) , and $Z_2 \sim \text{Bernoulli}(p = 0.3)$, with corresponding parameters (α_2, β_2) . The logistic regression part also includes an intercept α_0 .

We begin by generating a larger sample than we desire to account for those who will be left out due to truncation. Values for α are chosen to procure the desired percentage of cured individuals on average in the population, and we refer to this as the % of cured individuals in a simulation study. An individual is designated as either cured or not with the probability determined from the logistic model.

The baseline survival function for the Cox model is set as $S_0(t) = 20 - t$, the survival function of a Uniform $(0, 20)$ random variable. The baseline cumulative hazard is thus $\Lambda_0(t) = 20\{1 - e^{-t}\}$. For those not cured individuals we generate an event time $T = 20\{1 - U^{\exp(-\beta_1 Z_1 - \beta_2 Z_2)}\}$, where $U \sim \text{Uniform}(0, 1)$.

Truncation times are generated from Uniform $(0, a)$ for some $a < 15$ chosen so that on average the desired percentage of uncured individuals are truncated out. We refer to this percentage as the % of truncation. Once the truncation times are generated, all individuals with event times less than their truncation times are removed, and we reduce the data set to the desired sample size by taking the first n individuals from those who remain. Finally, when there is censoring the censoring times are generated from Uniform $(15, b)$ for some $b > 20$ so that on average the desired percentage of the n individuals (including those who are cured) will have a censoring time less than $\min(T_i, 20)$. We refer to this percentage as the % of censoring. We ran all simulations with 500 trials below.

4.2 Simulation results

In Tables 1 we examine the performance of the NPMLE. We consider a smaller sample size $n = 200$ and a larger sample size $n = 1000$, and like in the pregnancy studies for SAB we assume that a majority 75% of the subjects are cured. We ran simulations over the combination of two truncation scenarios (10%, 20%) and two censoring scenarios (0%, 20%). In the tables we provide the average parameter estimates (“Estimate”), the sample standard deviation of these estimates over the 500 simulation trials (“Sample SD”), the mean over the 500 trials of the standard errors based on our variance estimation (“SE”), and the empirical coverage probabilities (“Coverage”) of the nominal 95% confidence intervals using the SE’s.

According to the table, the performance of NPMLE is quite good. The average estimates of the parameters are generally close to their true values in all scenarios. This includes for the Cox part of the model under the smaller sample size $n = 200$, where only about 25% of the sample have events when there is no censoring, and even fewer in the presence of censoring. The variance estimator generally improves with larger sample size, especially for the Cox part of the model and with 20% censoring, which

also reflects in the coverage probabilities of the nominal 95% confidence intervals. Note that with 500 simulation trials these empirical coverage probabilities have about $\pm 2\%$ margin of error.

5 Analysis of spontaneous abortion data

The data we investigate come from the OTIS autoimmune disease in pregnancy database as mentioned earlier. Our sample includes pregnant women who entered a research study between 2005 and 2012. It consists of $n = 929$ women who entered the study before week 20 of their gestation, with complete covariate information. Among them 482 (52%) were pregnant women with certain autoimmune diseases who were treated with medications under investigation, 265 (28%) were women with the same specific autoimmune diseases who were not treated with the medications under investigation, and the rest 182 (20%) were healthy pregnant women without autoimmune diseases who were not treated with the medications. Chambers *et al.* (2001) discussed the importance of having a diseased control group, since some of the adverse outcomes in pregnancy may be due to the diseases instead of the medications. There were a total of 66 SAB events, and 2 women were lost to follow up before 20 weeks of gestation.

There are a number of risk factors for spontaneous abortion that have been identified in the literature (Chambers *et al.*, 2013, for example). Alternatively, we can use a data driven selection method for risk factors in our cure rate model. For each baseline covariate, we use the Wald test with two degrees of freedom for both coefficients in the logistic and the Cox part of the model. We first screen the covariates with a univariate cure rate model, with a p -value cutoff of 0.2 for the Wald test. We then run a backward selection, with a p -value cutoff of 0.1 for the Wald test. The selected variables are body mass index (BMI) group (0: BMI < 18.5, 1: BMI \in [18.5,24.9), 2: BMI \in [25,29.9]), 3: BMI > 30) treated as numerical due to small number of total SAB events, gravidity > 1 or not, i.e. whether a woman had been previously pregnant, whether there was

smoking (Y/N) or alcohol (Y/N) intake during early pregnancy. We fit our final cure model to the data with these covariates and exposure status, and the results using the NPMLE are given in Table 2 left columns.

From Table 2, we see that larger body mass index significantly decreases the probability of SAB in the logistic part of the model. The probability of SAB of either healthy control group or disease control group is not significantly different from the medication exposed women. The Cox regression part of the model identified all four covariates as significant factors for the hazard of SAB. In the cure model context since the Cox model is only used for those who eventually have events (observed or censored), this part of the model should be understood as impact of the covariates on the timing of SAB; that is, significantly later timing of SAB for those who had larger body mass index, gravidity > 1 or smoking, and significantly earlier timing for those who had alcohol. Figure 2 illustrates the significance (or not) of BMI and alcohol in association with the overall risk of SAB by 20 weeks of gestation as well as with the timing of SAB among those women not observed to be cured.

Accounting for the left truncation, classical survival analysis methods including the Cox proportional hazards regression model have been advocated in the literature (Meister and Schaefer, 2008; Xu and Chambers, 2011). As a comparison, Table 2 right columns (lower half) show the results of the classic Cox regression model fitted to the data by treating all the cured individuals as right-censored at 20 weeks of gestation, as is currently done in the practical analysis of SAB data (Chambers *et al.*, 2013). Gravidity and smoking are no longer significant predictors of SAB. Note that under the proportional hazards assumption, nonsignificant effects of gravidity or smoking translates to no significant differences in the cumulative risks of SAB; that is, the impact on the timing of SAB is no longer distinguished from the impact on the overall cumulative risk of SAB (Y/N) by 20 weeks of gestation. In addition, as mentioned before, treating the majority of the women (who did not have SAB) as right-censored

can lead to substantial loss of information.

Finally we also fit the ‘naive’ logistic regression model alone to the data, using whether a woman has SAB (Y/N) as the outcome. The results are also given in the right columns (upper half) of Table 2. We note that this model does not properly handle left truncation, and results are wildly different from the other model fits and should be not trusted.

6 Discussion and Conclusion

In this paper we have developed an NPMLE approach to fit the mixture type cure rate models to data with left truncation in addition to right-censoring. As illustrated in the data analysis, the cure rate model methodology developed here is able to make use of the information from both the women who had SAB and those who were observed not to have SAB, as well as to separate the differential regression effects of the covariates on both the cumulative risk of SAB as well as the timing of it among those who experience SAB. We anticipate this methodology to impact the practical analysis of pregnancy and other similar types of data. An ‘alpha’ version of a corresponding R package is currently being tested internally.

Different from the usual cure rate data where the long-term survivors are always right-censored, in our pregnancy studies we observe the majority of the ‘cured’ women. This greatly improves the practical identifiability of the cured portion (Sy and Taylor, 2000; Lu and Ying, 2004), as well as substantially increases the amount of information available for estimating the model parameters. Our inference procedures utilize the NPMLE, together with the “ghost copy” EM algorithm to produce estimators for the model parameters. The variances of the estimators can be obtained in closed form using the Louis (1982) formula. In our simulations, the variance estimator leads to relatively accurate coverage of the 95% confidence intervals.

In our proof for consistency, we have worked through an unbounded cumulative

baseline hazard, which has rarely been discussed in existing literatures. Ideally, we would like to show asymptotic normality without assuming the interval-censoring tail window. However, the weak convergence of nonparametric estimators often requires a stronger set of assumptions. As a result, the unbounded Λ_0 in the log-likelihood causes trouble in the Fréchet differentiability and continuously invertibility steps. The “chop-off” argument applied in consistency does not work here as Λ_0 appear in both the parametric part and the nonparametric part of the directional score.

Finally for left truncated data much work has been done recently under the length-biased assumption (Asgharian *et al.*, 2006; Ning *et al.*, 2010; Qin *et al.*, 2011, among others). For enrollment into observational pregnancy studies like ours, we do not think that the uniform distributional assumption necessarily holds, as is evident in Figure 1. However, it would be of interest to compare the efficiency (as well as bias) of the different approaches, and to develop methods under other parametric assumptions that are more suitable for the entry times to pregnancy studies.

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A Appendix A: Proofs

A.1 The Existence of NPMLE

Proof of Theorem 1. Let θ_B be the maximizer on the compliment of compact set $\{\|\boldsymbol{\alpha}\| \vee \|\boldsymbol{\beta}\| \vee \|\boldsymbol{\lambda}\| \leq B\}$. We show that $l(\theta_B) \rightarrow -\infty$ when $B \rightarrow \infty$.

By Assumptions 1 and 2, we have the bound (12).

All terms in the log-likelihood are bounded except for

$$\sum_{i=1}^n \left\{ \delta_i^1 \log \lambda(X_i) - \delta_i^1 e^{\boldsymbol{\beta}^\top \mathbf{z}_{2i}} \Lambda(X_i) \right\}.$$

Let λ_{\max} be the largest element in $\boldsymbol{\lambda}$. The expression above has the upper bound

$$\log(\lambda_{\max}/m) - \lambda_{\max}/m - K \log m,$$

which diverges to $-\infty$ when we set $B \rightarrow \infty$.

Then, the global maximizer must be in one of the compact set $\{\|\boldsymbol{\alpha}\| \vee \|\boldsymbol{\beta}\| \vee \|\boldsymbol{\lambda}\| \leq B^*\}$ for some $B^* > 0$. \square

Let $W_i^\theta(t)$ be defined as in (16). We define a generic inequality to be referenced later, for any $\boldsymbol{\theta} = (\boldsymbol{\alpha}, \boldsymbol{\beta}, \Lambda)$ in the parameter space whose baseline cumulative hazard Λ is a step function jumping only at the observed event times, t_1, \dots, t_K :

$$0 < d\Lambda(t_k) \leq \left(\sum_{j=1}^n W_j^\theta(t_k) e^{\boldsymbol{\beta}^\top \mathbf{z}_{2j}} \right)^{-1} d\bar{N}(t_k), \quad k = 1, \dots, K. \quad (\text{A1})$$

The conclusion of the following Lemma is used in the proofs of both Lemma 1 and Theorem 3.

Lemma A1. *Let $\boldsymbol{\theta}_{(n)} = (\boldsymbol{\alpha}_{(n)}, \boldsymbol{\beta}_{(n)}, \Lambda_{(n)})$ be a sequence in the parameter space where $\Lambda_{(n)}$ is a non-decreasing step function with jumps only at the observed event times. Suppose that $\boldsymbol{\theta}_{(n)}$ satisfies (A1) and has a subsequence $\boldsymbol{\theta}_{(n_k)}$ converging to a limiting point $\boldsymbol{\theta}^* = (\boldsymbol{\alpha}^*, \boldsymbol{\beta}^*, \Lambda^*)$ a.s.:*

$$\boldsymbol{\alpha}_{(n_k)} - \boldsymbol{\alpha}^* \rightarrow 0, \quad \boldsymbol{\beta}_{(n_k)} - \boldsymbol{\beta}^* \rightarrow 0, \quad \sup_{t \in [0, \tau]} |e^{-\Lambda_{(n_k)}(t)} - e^{-\Lambda^*(t)}| \rightarrow 0, \quad \text{a.s..} \quad (\text{A2})$$

Under Assumptions 1 - 4,

a) $\Lambda^*(t) < \infty$ for all $t < \tau$;

b) $\inf_{t \in [0, \zeta]} E[W^{\theta^*}(t)e^{\beta^{*\top} \mathbf{Z}_2}] > C_w$, for some $C_w > 0$.

Proof of Lemma A1. By checking the uniform continuity of $W_i^{\theta}(t)e^{\beta^\top \mathbf{Z}_{2i}}$ in $(\alpha, \beta, e^{-\Lambda(t)})$, we may establish

$$\sup_{t \in [0, \tau]} \left| W_i^{\theta^*}(t)e^{\beta^{*\top} \mathbf{Z}_{2i}} - W_i^{\theta(n_k)}(t)e^{\beta(n_k)^\top \mathbf{Z}_{2i}} \right| \rightarrow 0, \quad a.s..$$

$W_i^{\theta}(t)$ as a function of observed random variables belongs to a Glivenko-Cantelli class of uniformly bounded functions with uniformly bounded variation. Thus, the pointwise convergence can be strengthened to be uniform convergence,

$$\sup_{t \in [0, \tau]} \left| \frac{1}{n} \sum_{i=1}^{n_k} W_i^{\theta(n_k)}(t)e^{\beta(n_k)^\top \mathbf{Z}_{2i}} - E[W^{\theta^*}(t)e^{\beta^{*\top} \mathbf{Z}_2}] \right| \xrightarrow{a.s.} 0.$$

Note that $n^{-1} \sum_{i=1}^{n_k} W_i^{\theta(n_k)}(t)e^{\beta(n_k)^\top \mathbf{Z}_{2i}}$ is càglàd, so its limit $E[W^{\theta^*}(t)e^{\beta^{*\top} \mathbf{Z}_2}]$ must also be càglàd.

a) Let $\tau^* = \inf\{t \in [0, \zeta] : e^{-\Lambda^*(t)} = 0\}$. We shall prove that $\tau^* = \tau$.

Suppose that τ^* is an interior point of $[0, \tau]$. From Assumption 4, $d\Lambda_0([s, t]) = \Lambda_0(t) - \Lambda_0(s) > 0$ for any $s < t$ in $[0, \tau]$. By the definition of τ^* , $\Lambda^*(t) = \infty$ and $\phi^{\theta^*}(t) = 0$ for $t \in [\tau^*, \tau]$, so we have

$$E[W^{\theta^*}(\tau^*)e^{\beta^{*\top} \mathbf{Z}_2}] = E\left[\int_{\tau_-^*}^{\tau} e^{\beta^{*\top} \mathbf{Z}_2} dN(u)\right] > 0.$$

By the left continuity of $W_i^{\theta}(t)$, $\exists s < \tau^*$, s.t.

$$\inf_{t \in [s, \tau^*]} E[W^{\theta^*}(t)e^{\beta^{*\top} \mathbf{Z}_2}] \geq \frac{1}{2} E\left[\int_{\tau_-^*}^{\tau} e^{\beta^{*\top} \mathbf{Z}_2} dN(u)\right].$$

The total increment of $\Lambda(n_k)$ in $[s, \tau^*]$ must be bounded almost surely according to (A1).

By the definition of τ^* , $\Lambda^*(s) < \infty$. Putting these together, we reach the contradiction,

$$\begin{aligned} \Lambda^*(\tau^*) &\leq \overline{\lim}_{k \rightarrow \infty} \Lambda(n_k)(\tau^*) \leq \overline{\lim}_{k \rightarrow \infty} \Lambda(n_k)(s) + \int_{s+}^{\tau^*} \frac{d\bar{N}(u)}{\sum_{i=1}^{n_k} W_i^{\theta(n_k)}(u)e^{\beta(n_k)^\top \mathbf{Z}_{2i}}} \\ &\leq \Lambda^*(s) + \frac{\tau^* - s}{\inf_{t \in [s, \tau^*]} E[W^{\theta^*}(t)e^{\beta^{*\top} \mathbf{Z}_2}]} < \infty. \end{aligned}$$

The other case is $\tau^* = 0$. Then, $\Lambda^*(t) = \infty$ and $\phi^{\theta^*}(t) = 0$ for $t \in [0, \tau]$. The contradiction is easily established as

$$E \left[W^{\theta^*}(0) e^{\beta^{*\top} \mathbf{Z}_2} \right] = E \left[\int_0^\tau e^{\beta^{*\top} \mathbf{Z}_2} dN(u) \right] > 0.$$

b) Since $E[W^{\theta^*}(t) e^{\beta^{*\top} \mathbf{Z}_2}]$ is càglàd, $\theta_{(n_k)}$ satisfies (A1) and converges uniformly to θ^* , it can be seen that $E[W^{\theta^*}(t) e^{\beta^{*\top} \mathbf{Z}_2}] \geq 0$ over the interior of $[0, \zeta]$.

Write $n_k^{-1} \sum_{i=1}^{n_k} W_i^{\theta}(t) e^{\beta^\top \mathbf{Z}_{2i}}$ as

$$\begin{aligned} & n_k^{-1} \sum_{i=1}^{n_k} \int_{t-}^{\tau} \{1 - \phi_i^{\theta}(u)\} e^{\beta^\top \mathbf{Z}_{2i}} dN_i(u) + \int_t^{\tau} Y_i(u) e^{\beta^\top \mathbf{Z}_{2i}} d\phi_i^{\theta}(u) + Y_i(t) \phi_i^{\theta}(t) e^{\beta^\top \mathbf{Z}_{2i}} \\ &= n_k^{-1} \sum_{i=1}^{n_k} \int_{t+}^{\tau} \left[1 - \phi_i^{\theta}(u) - \frac{\sum_{j=1}^{n_k} Y_j(u) \phi_j^{\theta}(u) \{1 - \phi_j^{\theta}(u)\} e^{\beta^\top \mathbf{Z}_{2j}}}{\sum_{j=1}^{n_k} W_j^{\theta}(u) e^{\beta^\top \mathbf{Z}_{2j}}} \right] e^{\beta^\top \mathbf{Z}_{2i}} dN_i(u) \\ & \quad + \{1 - \phi_i^{\theta}(t)\} e^{\beta^\top \mathbf{Z}_{2i}} dN_i(t) + Y_i(t) \phi_i^{\theta}(t) e^{\beta^\top \mathbf{Z}_{2i}}. \end{aligned} \tag{A3}$$

By Assumption 4, all $Q_i < \zeta$ a.s.. Thus,

$$\begin{aligned} E \left[W^{\theta^*}(\zeta) e^{\beta^{*\top} \mathbf{Z}_2} \right] &= E \left[\{\delta^1 + \delta^c \phi^{\theta^*}(X)\} I\{\zeta \leq X\} e^{\beta^{*\top} \mathbf{Z}_2} \right] \\ &\geq E \left[\int_{\zeta}^{\tau} e^{\beta^{*\top} \mathbf{Z}_2} dN(u) \right] > 0. \end{aligned}$$

For $t < \zeta$, the difference $E[W^{\theta^*}(t) e^{\beta^{*\top} \mathbf{Z}_2}] - E[W^{\theta^*}(\zeta) e^{\beta^{*\top} \mathbf{Z}_2}]$ is the limit of an integral like that in (A3), where the integrand has $\sum_{j=1}^{n_k} W_j^{\theta}(u) e^{\beta^\top \mathbf{Z}_{2j}}$ in the denominator. So it has potential singularities at the zeros of $E[W^{\theta^*}(u) e^{\beta^{*\top} \mathbf{Z}_2}]$ for $u \in [t, \zeta]$. We shall show that $E[W^{\theta^*}(u) e^{\beta^{*\top} \mathbf{Z}_2}]$ is differentiable with respect to $d\Lambda_0(u)$ in $[0, \zeta]$, so that its zero u_0 leads to the divergent form $-\int_t^\zeta |u - u_0|^{-1} du$. We will then reach the contradiction that $E[W^{\theta^*}(t) e^{\beta^{*\top} \mathbf{Z}_2}] = -\infty$, as seen below.

Denote R_0 the set of zeros and limiting zeros from right for $E[W^{\theta^*}(u) e^{\beta^{*\top} \mathbf{Z}_2}]$. Let set $R_{\Delta u}$ be the Δu neighborhood of R_0 and $\Omega_{\Delta u}^t = [t, \zeta] \setminus R_{\Delta u}$. $E[W^{\theta^*}(u) e^{\beta^{*\top} \mathbf{Z}_2}]$ is

bounded away from zero on $\Omega_{\Delta u}^t$. Through (A3),

$$\begin{aligned}
& E \left[W^{\boldsymbol{\theta}^*}(t) e^{\boldsymbol{\beta}^{*\top} \mathbf{Z}_2} \right] - E \left[W^{\boldsymbol{\theta}^*}(\zeta) e^{\boldsymbol{\beta}^{*\top} \mathbf{Z}_2} \right] \\
& \leq - \int_{\Omega_{\Delta u}^t} \frac{E[Y(u) \phi^{\boldsymbol{\theta}^*}(u) \{1 - \phi^{\boldsymbol{\theta}^*}(u)\} e^{\boldsymbol{\beta}^{*\top} \mathbf{Z}_2}]}{E[W^{\boldsymbol{\theta}^*}(u) e^{\boldsymbol{\beta}^{*\top} \mathbf{Z}_2}]} E \left[e^{\boldsymbol{\beta}^{*\top} \mathbf{Z}_2} dN(u) \right] \\
& + E \left[\int_{t+}^{\zeta} \{1 - \phi^{\boldsymbol{\theta}^*}(u)\} dN(u) + \{1 - \phi^{\boldsymbol{\theta}^*}(t)\} e^{\boldsymbol{\beta}^{*\top} \mathbf{Z}_2} dN(t) + Y(t) \phi^{\boldsymbol{\theta}^*}(t) e^{\boldsymbol{\beta}^{*\top} \mathbf{Z}_2} \right].
\end{aligned} \tag{A4}$$

From part **a)**, $e^{-\Lambda^*(\zeta)} > 0$. For any $u < \zeta$,

$$\phi_i^{\boldsymbol{\theta}^*}(u) \geq \phi_i^{\boldsymbol{\theta}^*}(\zeta) \geq \frac{m^{-1} e^{-m\Lambda^*(\zeta)}}{1 + m^{-1} e^{-m\Lambda^*(\zeta)}} > 0.$$

So the limit of numerator term $E[Y(u) \phi^{\boldsymbol{\theta}^*}(u) \{1 - \phi^{\boldsymbol{\theta}^*}(u)\} e^{\boldsymbol{\beta}^{*\top} \mathbf{Z}_2}]$ is bounded away from zero. And $\forall u \in [0, \zeta]$,

$$\begin{aligned}
\left| \frac{dEW^{\boldsymbol{\theta}^*}(u)}{d\Lambda_0(u)} \right| &= \left| E \left[\{1 - \phi^{\boldsymbol{\theta}^*}(u)\} Y(u) \phi^{\boldsymbol{\theta}^*}(u) e^{\boldsymbol{\beta}_0^{\top} \mathbf{Z}_2} - \phi^{\boldsymbol{\theta}^*}(u) \frac{dE[Y(u) | \mathbf{Z}_1, \mathbf{Z}_2]}{d\Lambda_0(u)} \right] \right| \\
&\leq m + \mathcal{L} < \infty.
\end{aligned}$$

The first term in (A4) diverges to $-\infty$ when $\Delta u \rightarrow 0$. The other terms are bounded, so this is the desired contradiction. □

Proof of Lemma 1. For any $\boldsymbol{\theta}$ denote $\lambda_{\max, \zeta} = \max\{\lambda_k : t_k \leq \zeta\}$, where ζ is the upper bound of truncation time defined in Assumption 4. Define a set in the parameter space:

$$\Theta = \{ \boldsymbol{\theta} = (\boldsymbol{\alpha}, \boldsymbol{\beta}, \Lambda) | \lambda_{\max, \zeta} \leq n^{-1} 2 / C_w \}, \tag{A5}$$

with C_w defined in Lemma A1. We would like to show that

$$\lim_{n \rightarrow \infty} P(\hat{\boldsymbol{\theta}}, \tilde{\boldsymbol{\theta}} \in \hat{\Theta}) = 1. \tag{A6}$$

This is done through applying Lemma A1, so we will need to verify condition (A1) for $\tilde{\boldsymbol{\theta}}$ and $\hat{\boldsymbol{\theta}}$.

First, define the marginal of the complete data likelihood

$$\begin{aligned}\tilde{L}(\boldsymbol{\theta}) &= \sum_{A_i=0,1} \sum_{M_i=0}^{\infty} \sum_{\tilde{T}_{i1}=t_k:t_k \leq Q_i} \cdots \sum_{\tilde{T}_{iM_i}=t_k:t_k \leq Q_i} L_i^c(\boldsymbol{\theta}) \\ &= \prod_{i=1}^n \frac{\{p_i \lambda_i(X_i) S_i(X_i)\}^{\delta_i^1} (1-p_i)^{\delta_i^0} \{p_i S_i(X_i) + 1-p_i\}^{\delta_i^c}}{1 - p_i \sum_{k:t_k \leq Q_i} \lambda_k e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} S_i(t_k)}.\end{aligned}$$

From (2) it can be seen that the complete data likelihood $L^c(\boldsymbol{\theta})$ can be decomposed into the product of one logistic part concave in $\boldsymbol{\alpha}$ with one Cox part concave in $(\boldsymbol{\beta}, \boldsymbol{\lambda})$. Thus, it is concave in $\boldsymbol{\theta}$. $\tilde{L}(\boldsymbol{\theta})$ is also concave as the sum over concave functions.

Next we show that the EM finds the unique stationary point of $\tilde{L}(\boldsymbol{\theta})$, which then must be the global maximizer since it is concave. Consider the conditional expectation given the observed data as in (5) - (7). It can be verified directly (we skip the algebraic details here) that:

$$\nabla \log \tilde{L}(\boldsymbol{\theta}) = E_{\boldsymbol{\theta}}[\nabla \log L^c(\boldsymbol{\theta}) | \mathcal{O}].$$

The estimator $\tilde{\boldsymbol{\theta}}$ is by definition the solution to the left-hand side of the above being zero, hence also the stationary point of $\tilde{L}(\boldsymbol{\theta})$.

We write down the stationary equation $\boldsymbol{\theta}^{(l)} = \boldsymbol{\theta}^{(l+1)} = \tilde{\boldsymbol{\theta}}$ for $\tilde{\lambda}_k$'s at convergence,

$$\tilde{\lambda}_k = \frac{1 + \tilde{\lambda}_k \sum_{i=1}^n \frac{\tilde{p}_i e^{\tilde{\boldsymbol{\beta}}^\top \mathbf{Z}_{2i}} \tilde{S}_i(t_k) I(Q_i \geq t_k)}{1 - \tilde{p}_i \sum_{h:h < Q_i} \tilde{f}_i(t_h)}}{\sum_{i=1}^n \left\{ \delta_i^1 I(X_i \geq t_k) + \delta_i^c \phi_i^{\tilde{\boldsymbol{\theta}}}(X_i) I(X_i \geq t_k) + \sum_{j \geq k} \frac{\tilde{p}_i \tilde{f}_i(t_j) I(Q_i \geq t_j)}{1 - \tilde{p}_i \sum_{h:h < Q_i} \tilde{f}_i(t_h)} \right\} e^{\tilde{\boldsymbol{\beta}}^\top \mathbf{Z}_{2i}}},$$

where f_i was previously defined just above (3). Combining $\tilde{\lambda}_k$ terms leads to

$$\begin{aligned}\tilde{\lambda}_k^{-1} &= \sum_{i=1}^n \left\{ \delta_i^1 I(X_i \geq t_k) + \delta_i^c \phi_i^{\tilde{\boldsymbol{\theta}}}(X_i) I(X_i \geq t_k) \right. \\ &\quad \left. - \tilde{p}_i \frac{\tilde{S}_i(t_k) I(Q_i \geq t_k) - \sum_{j \geq k} \tilde{f}_i(t_j) I(Q_i \geq t_j)}{1 - \tilde{p}_i \sum_{h:h < Q_i} \tilde{f}_i(t_h)} \right\} e^{\tilde{\boldsymbol{\beta}}^\top \mathbf{Z}_{2i}}.\end{aligned}\quad (\text{A7})$$

By the mean value theorem,

$$0 \leq e^{\lambda_k e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}}} - 1 - \lambda_k e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \leq \frac{1}{2} \left(\lambda_k e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right)^2 e^{\lambda_k e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}}} \leq \frac{1}{2} m^2 \lambda_k^2 e^{\lambda_k m}. \quad (\text{A8})$$

where m is defined in (12). Applying (A8) to the denominator in (A7), we get

$$1 - \tilde{p}_i \sum_{h:h < Q_i} \tilde{f}_i(t_h) \geq 1 - \tilde{p}_i \{1 - \tilde{S}_i(Q_i)\}.$$

By a similar argument, we have almost surely

$$\begin{aligned}
& \tilde{S}_i(t_k)I(Q_i \geq t_k) - \sum_{j \geq k} \tilde{f}_i(t_j)I(Q_i \geq t_j) \\
&= \tilde{S}_i(Q_i)I(Q_i \geq t_k) + \sum_{j \geq k} \left\{ 1 - e^{-\tilde{\lambda}_j e^{\tilde{\beta}^\top \mathbf{Z}_{2i}}} - \tilde{\lambda}_j e^{\tilde{\beta}^\top \mathbf{Z}_{2i}} \right\} \tilde{S}_i(t_j)I(Q_i > t_j) \\
&\leq \tilde{S}_i(Q_i)I(Q_i \geq t_k).
\end{aligned}$$

Then, $\tilde{\boldsymbol{\theta}}$ satisfies (A1).

For $\hat{\boldsymbol{\theta}}$, it must satisfy the score equation for λ_k 's:

$$\frac{\partial l(\boldsymbol{\theta})}{\partial \lambda_k} = \sum_{i=1}^n \left\{ \frac{dN_i(t_k)}{\lambda_k} - W_i^{\boldsymbol{\theta}}(t_k) e^{\beta^\top \mathbf{Z}_{2i}} \right\} = 0, \quad \forall k = 1, \dots, K.$$

This is the equation version of (A1) after rearrangement.

Now let $\hat{\lambda}_{\max, \zeta}$ and $\tilde{\lambda}_{\max, \zeta}$ be the largest jump for $\hat{\Lambda}$ and $\tilde{\Lambda}$ on $[0, \zeta]$, correspondingly.

By Lemma A1 part **b**), we have

$$\limsup_{n \rightarrow \infty} n \hat{\lambda}_{\max, \zeta} \leq C_w^{-1}, \quad \limsup_{n \rightarrow \infty} n \tilde{\lambda}_{\max, \zeta} \leq C_w^{-1}, \text{ a.s.}$$

Hence (A6) is established.

In the set Θ , we evaluate the discrepancy between $\log \tilde{L}(\boldsymbol{\theta})$ and $\log L(\boldsymbol{\theta})$, which can be bounded as following

$$1 - S_i(Q_i) - \sum_{k: t_k < Q_i} \lambda_k e^{\beta^\top \mathbf{Z}_{2i}} S_i(t_k) = \sum_{k: t_k < Q_i} S_i(t_k) \left(e^{\lambda_k e^{\beta^\top \mathbf{Z}_{2i}}} - 1 - \lambda_k e^{\beta^\top \mathbf{Z}_{2i}} \right). \quad (\text{A9})$$

Applying (A8) to $|\log L(\boldsymbol{\theta}) - \log \tilde{L}(\boldsymbol{\theta})|$, we have the bound

$$\begin{aligned}
\left| \log L(\boldsymbol{\theta}) - \log \tilde{L}(\boldsymbol{\theta}) \right| &\leq \sum_{i=1}^n \left| \log \{1 - p_i + p_i S_i(Q_i)\} - \log \left\{ 1 - p_i \sum_{k: t_k < Q_i} \lambda_k e^{\beta^\top \mathbf{Z}_{2i}} S_i(t_k) \right\} \right| \\
&\leq \sum_{i=1}^n \left| \frac{p_i}{1 - p_i} \frac{n}{2} m^2 \lambda_k^2 e^{\lambda_k m} \right| \leq \frac{1}{2} n^2 e^{m \lambda_{\max, \zeta}} m^3 \lambda_{\max, \zeta}^2.
\end{aligned}$$

Using the upper bound for $\lambda_{\max, \zeta}$ in Θ , we can bound

$$\sup_{\boldsymbol{\theta} \in \Theta} \left| \log L(\boldsymbol{\theta}) - \log \tilde{L}(\boldsymbol{\theta}) \right| \leq e^{\frac{2m}{C_w}} \frac{2m^3}{C_w^2}. \quad (\text{A10})$$

In summary whenever $\hat{\boldsymbol{\theta}}, \tilde{\boldsymbol{\theta}} \in \Theta$, we have

$$0 \leq \log L(\hat{\boldsymbol{\theta}}) - \log L(\tilde{\boldsymbol{\theta}}) \leq \log L(\hat{\boldsymbol{\theta}}) - \log \tilde{L}(\hat{\boldsymbol{\theta}}) + \log \tilde{L}(\tilde{\boldsymbol{\theta}}) - \log L(\tilde{\boldsymbol{\theta}}) < e^{\frac{2m}{C_w}} \frac{4m^3}{C_w^2}. \quad (\text{A11})$$

Combining (A11) and (A6) completes the proof. \square

Proof of Theorem 2 and 2'. From Lemma 1, we only need to establish the following two facts: 1) $E[l_1(\boldsymbol{\theta})]$ exists with one unique maximal, and 2) it is locally invertible at the maximal. We will see that 1) is verified through the proof of Theorem 3, and 2) is verified through the proof of Theorem 4. \square

A.2 Consistency of NPMLE

Proof of Theorem 3. The constants m , c , ε and \mathcal{L} are defined in (12), (13) and (14).

First, we show that the “bridge” $\bar{\Lambda}$ defined in (17) converges to the true Λ_0 in the following sense:

$$\sup_{t \in [0, \tau]} \left| e^{-\bar{\Lambda}(t)} - e^{-\Lambda_0(t)} \right| \rightarrow 0, a.s. \quad (\text{A12})$$

as $n \rightarrow \infty$. We have the bound for $\forall t \in (0, \tau)$,

$$m \geq \frac{E \left[Y(t) \phi^{\boldsymbol{\theta}_0}(t) e^{\boldsymbol{\beta}_0^\top \mathbf{Z}_2} \right]}{E \left[\log \left\{ 1 + \exp \left(\boldsymbol{\alpha}_0^\top \mathbf{Z}_1 - \Lambda_0(t) e^{\boldsymbol{\beta}_0^\top \mathbf{Z}_{2i}} \right) \right\} \right]} \geq \frac{\varepsilon}{m^2 + m}. \quad (\text{A13})$$

For any $\tau^* < \tau$ in \mathbb{Q} the set of rational numbers, $E[Y(t) \phi^{\boldsymbol{\theta}_0}(t) e^{\boldsymbol{\beta}_0^\top \mathbf{Z}_2}]$ is bounded away from zero over $[0, \tau^*]$. The uniform convergence of $\bar{\Lambda}$ to Λ_0 over any $[0, \tau^*]$ can be obtained in the way like Murphy (1994). To extend the result to (A12), we use a trick described in (A14)-(A17). By Assumption 3, Λ_0 is non-decreasing and diverges to ∞ at τ . Therefore,

$$\forall \epsilon > 0, \exists \tau^* \in (0, \tau) \cap \mathbb{Q}, s.t. e^{-\Lambda_0(\tau^*)} < \epsilon/3. \quad (\text{A14})$$

Through Rao’s law of large number and Helly-Bray argument, we have

$$\sup_{t \in [0, \tau^*]} |\bar{\Lambda}(t) - \Lambda_0(t)| \rightarrow 0, \quad a.s.. \quad (\text{A15})$$

By continuity of the exponential function,

$$\exists N, \forall n > N, \sup_{t \in [0, \tau^*]} |e^{-\bar{\Lambda}(t)} - e^{-\Lambda_0(t)}| < \epsilon/3. \quad (\text{A16})$$

Then,

$$\forall n > N, \sup_{t \in [\tau^*, \tau]} |e^{-\bar{\Lambda}(t)} - e^{-\Lambda_0(t)}| \leq 2e^{-\Lambda_0(\tau^*)} + |e^{-\bar{\Lambda}(\tau^*)} - e^{-\Lambda_0(\tau^*)}| < \epsilon. \quad (\text{A17})$$

Therefore, we have proved (A12).

Next, we evaluate the difference between the limits of $\hat{\Lambda}$ and $\bar{\Lambda}$. According to Assumption 1 and $e^{-\hat{\Lambda}(t)} \in [0, 1]$, $(\hat{\alpha}, \hat{\beta}, e^{-\hat{\Lambda}(t)})$ is bounded. $\hat{\Lambda}(t)$ is Càdlàg, so is $e^{-\hat{\Lambda}(t)}$. By Helly's Selection theorem, there is a subsequence converging uniformly almost surely to some $\theta^* = (\alpha^*, \beta^*, e^{-\Lambda^*})$. Lemma A1 part **b)** gives the bound for $E\{W^\theta(t)e^{\beta^\top \mathbf{Z}_2}\}$ over $[0, \zeta]$. We only need to find its bound on $[\zeta, \tau]$ in order to mimic the proof of Lemma 1 of Murphy (1994). Note that

$$\begin{aligned} E[W^\theta(t)e^{\beta^\top \mathbf{Z}_2}] &= E\left[\int_{t-}^{\tau} \{1 - \phi^\theta(u)\} e^{\beta^\top \mathbf{Z}_2} dN(u)\right] \\ &\quad - E\left[\int_t^{\tau} \phi^\theta(u) e^{\beta^\top \mathbf{Z}_2} dE[Y(u)|\mathbf{Z}_1, \mathbf{Z}_2]\right]. \end{aligned}$$

By Assumption 4, $P(Q_i \leq \zeta) = 1$, so $E[Y(u)|\mathbf{Z}_1, \mathbf{Z}_2]$ is decreasing on $[\zeta, \tau]$. Along with the Lipschitz continuity, we have for $\forall t \in [\zeta, \tau]$

$$M\mathcal{L} \geq \frac{E[W^\theta(t)e^{\beta^\top \mathbf{Z}_2}]}{E\left[\log\left\{1 + \exp\left(\alpha_0^\top \mathbf{Z}_1 - \Lambda_0(t)e^{\beta_0^\top \mathbf{Z}_{2i}}\right)\right\}\right]} \geq \frac{\varepsilon}{m^2 + m}.$$

Therefore, $\gamma(t) = \frac{E[W^{\theta_0}(t)e^{\beta^\top \mathbf{Z}_2}]}{E[W^{\theta^*}(t)e^{\beta^{*\top} \mathbf{Z}_2}]}$ is bounded away from both ∞ and zero, and

$$\sup_{t \in [0, \tau]} \left| \frac{d\hat{\Lambda}}{d\bar{\Lambda}}(t) - \gamma(t) \right| \rightarrow 0 \text{ and } \sup_{t \in [0, \tau^*]} \left| \hat{\Lambda}(t) - \int_0^t \gamma d\Lambda_0 \right| \rightarrow 0 \text{ a.s., } \forall \tau^* < \tau \text{ in } \mathbb{Q}. \quad (\text{A18})$$

After all these preparation, we can use the semi-parametric Kullback-Leibler diver-

gence argument from Murphy (1994). We have

$$\begin{aligned}
0 &\leq \frac{1}{n} \{l_n(\hat{\alpha}, \hat{\beta}, \hat{\Lambda}) - l_n(\alpha_0, \beta_0, \bar{\Lambda})\} \\
&= \frac{1}{n} \sum_{i=1}^n \int_0^\tau \log \left\{ \frac{\phi_i^{\hat{\theta}}(u) e^{\hat{\beta}^\top \mathbf{Z}_{2i}} d\hat{\Lambda}(u)}{\phi_i^{\theta_0}(u) e^{\beta_0^\top \mathbf{Z}_{2i}} d\bar{\Lambda}(u)} \right\} \left\{ dN_i(u) - \phi_i^{\theta_0}(u) Y_i(u) e^{\beta_0^\top \mathbf{Z}_{2i}} d\bar{\Lambda}(u) \right\} \\
&\quad + \int_0^\tau \left[\log \left\{ \frac{\phi_i^{\hat{\theta}}(u) e^{\hat{\beta}^\top \mathbf{Z}_{2i}} d\hat{\Lambda}(u)}{\phi_i^{\theta_0}(u) e^{\beta_0^\top \mathbf{Z}_{2i}} d\bar{\Lambda}(u)} \right\} - \left\{ \frac{\phi_i^{\hat{\theta}}(u) e^{\hat{\beta}^\top \mathbf{Z}_{2i}} d\hat{\Lambda}(u)}{\phi_i^{\theta_0}(u) e^{\beta_0^\top \mathbf{Z}_{2i}} d\bar{\Lambda}(u)} - 1 \right\} \right] \\
&\quad \times \phi_i^{\theta_0}(u) e^{\beta_0^\top \mathbf{Z}_{2i}} Y_i(u) d\bar{\Lambda}(u). \tag{A19}
\end{aligned}$$

Denote the function in the logarithm above as $\psi_i(u)$. Using the definition of $\bar{\Lambda}$, we can rewrite the first term in (A19) as

$$\begin{aligned}
&\frac{1}{n} \sum_{i=1}^n \left\{ \int_0^\tau \log(\psi_i(u)) - \frac{\sum_{j=1}^n \log(\psi_j(u)) \phi_j^{\theta_0}(u) Y_j(u) e^{\beta_0^\top \mathbf{Z}_{2j}}}{\sum_{j=1}^n \phi_j^{\theta_0}(u) Y_j(u) e^{\beta_0^\top \mathbf{Z}_{2j}}} \right\} dN_i(u) \\
&= \frac{1}{n} \sum_{i=1}^n \left\{ \int_0^\tau \log(\psi_i(u)) - \frac{\sum_{j=1}^n \log(\psi_j(u)) \phi_j^{\theta_0}(u) Y_j(u) e^{\beta_0^\top \mathbf{Z}_{2j}}}{\sum_{j=1}^n \phi_j^{\theta_0}(u) Y_j(u) e^{\beta_0^\top \mathbf{Z}_{2j}}} \right\} dM_i(u) \tag{A20}
\end{aligned}$$

Inside $\psi_i(u)$, the ratio $d\hat{\Lambda}/d\bar{\Lambda}$ is bounded away from 0 and ∞ according to (A18). Denote the range of the ratio as $[1/R, R]$. The $\phi_i^{\theta_0}(u)$ term and $\phi_i^{\hat{\theta}}(u)$ term in $\psi_i(u)$ creates potential singularity for (A20) at τ , but its decay rate is bounded by $e^{-mR\Lambda_0(u)}$ by Assumptions 1 and 2. The integrands of martingale integral (A20) are all bounded a.s., and the quadratic variation of (A20) is bounded a.s. by

$$\frac{1}{n^2} \sum_{i=1}^n \int_0^\tau 4 \{mR\Lambda_0(u) + \log(R)\}^2 \phi_i^{\theta_0}(u) Y_i(u) e^{\beta_0^\top \mathbf{Z}_{2i}} d\Lambda_0(u).$$

It is of order $O_p(1/n)$, so the limit of (A20) is zero almost surely.

The integrands in the second term of (A19) is of the form $\log(x) - (x - 1) \leq 0$. In order to satisfy the inequality in (A19), we must have

$$\lim_{n \rightarrow \infty} \frac{1}{n} \sum_{i=1}^n \int_0^\tau \{ \log(\psi_i(u)) - (\psi_i(u) - 1) \} \phi_i^{\theta_0}(u) e^{\beta_0^\top \mathbf{Z}_{2i}} Y_i(u) d\bar{\Lambda}(u) = 0.$$

Applying the same argument as in Murphy (1994), we get

$$E \left(\int_0^\tau \left| \phi^{\theta^*}(u) e^{\beta^{*\top} \mathbf{Z}_2} \gamma(u) - \phi^{\theta_0}(u) e^{\beta_0^\top \mathbf{Z}_2} \right| Y(u) d\Lambda_0(u) \right) = 0 \tag{A21}$$

in the almost sure set. The identifiability of our model is verified in Li *et al.* (2001) Theorem 2. Along with our regularity conditions in Assumptions 2 and 3, (A21) leads to $\alpha^* = \alpha_0$, $\beta^* = \beta_0$ and $\gamma(t) = 1$. This implies that

$$\sup_{t \in [0, \tau^*]} \left| \hat{\Lambda}(t) - \Lambda_0(t) \right| \rightarrow 0 \text{ a.s.}, \forall \tau^* < \tau \text{ in } \mathbb{Q}.$$

Repeating the trick in (A14)-(A17), we have

$$\sup_{t \in [0, \tau]} \left| e^{-\hat{\Lambda}(t)} - e^{-\Lambda_0(t)} \right| \rightarrow 0 \text{ a.s..}$$

Finally, we summarize all usage of almost sure arguments to ensure that intersection of all almost sure sets still has probability one under σ -additivity. The steps (A14)-(A17) involves one almost sure argument for each choice of τ^* . We preserve the almost sure property by restricting τ^* to be in the countable set \mathbb{Q} . One almost sure argument is made for Helly's selection theorem. In Lemma A1, we use the Glivenko-Cantelli Theorem to avoid the dependence on the choice of θ^* , so the almost sure argument is only applied once. Two more almost sure arguments are used in calculating the limit of the terms in (A19).

□

Proof of Theorem 3'. The proof is essentially the same as the proof of Theorem 3, so the details are omitted. In fact, it is less technical due to the boundedness of Λ_0 over $[0, \tau']$.

□

A.3 Asymptotic Normality

First, we provide the definition of several quantities below. In Theorem 4 $\sigma(\mathbf{h}) = (\sigma_a(\mathbf{h}), \sigma_b(\mathbf{h}), \sigma_\eta(\mathbf{h}))$ is

$$\begin{aligned}\sigma_a(\mathbf{h}) &= E \left[\mathbf{Z}_1 \left\{ - \int_0^{\tau'} K_1^{\theta_0}(\mathbf{h})(u) Y(u) d\phi^{\theta_0}(u) \right. \right. \\ &\quad \left. \left. + K_2^{\theta_0}(\mathbf{h}) Y(\tau') \phi^{\theta_0}(\tau') (1 - \phi^{\theta_0}(\tau')) \right\} \right], \\ \sigma_b(\mathbf{h}) &= E \left[\mathbf{Z}_2 \left\{ \int_0^{\tau'} K_1^{\theta_0}(\mathbf{h})(u) Y(u) e^{\beta_0^\top \mathbf{Z}_2} d[\Lambda_0(u) \phi^{\theta_0}(u)] \right. \right. \\ &\quad \left. \left. - K_2^{\theta_0}(\mathbf{h}) Y(\tau') e^{\beta_0^\top \mathbf{Z}_2} \Lambda_0(\tau') \phi^{\theta_0}(\tau') (1 - \phi^{\theta_0}(\tau')) \right\} \right], \\ \sigma_\eta(\mathbf{h}) &= E \left[e^{\beta_0^\top \mathbf{Z}_2} \left\{ K_1^{\theta_0}(\mathbf{h})(u) \phi^{\theta_0}(u) Y(u) - K_2^{\theta_0}(\mathbf{h}) Y(\tau') \phi^{\theta_0}(\tau') (1 - \phi^{\theta_0}(\tau')) \right. \right. \\ &\quad \left. \left. - \int_u^{\tau'} K_1^{\theta_0}(\mathbf{h})(s) \phi^{\theta_0}(s) (1 - \phi^{\theta_0}(s)) Y(s) e^{\beta_0^\top \mathbf{Z}_2} d\Lambda_0(s) \right\} \right], \quad (\text{A22})\end{aligned}$$

where

$$\begin{aligned}K_1^\theta(\mathbf{h})(u) &= \mathbf{a}^\top \mathbf{Z}_1 (1 - \phi^\theta(u)) + \mathbf{b}^\top \mathbf{Z}_2 \left\{ 1 - (1 - \phi^\theta(u)) \Lambda(u) e^{\beta^\top \mathbf{Z}_2} \right\} \\ &\quad + \eta(u) - (1 - \phi^\theta(u)) e^{\beta^\top \mathbf{Z}_2} \int_0^u \eta d\Lambda, \\ K_2^\theta(\mathbf{h}) &= \left\{ \mathbf{a}^\top \mathbf{Z}_1 - \mathbf{b}^\top \mathbf{Z}_2 \Lambda(\tau') e^{\beta^\top \mathbf{Z}_2} - \int_0^{\tau'} \eta e^{\beta^\top \mathbf{Z}_2} d\Lambda \right\}. \quad (\text{A23})\end{aligned}$$

Let $\boldsymbol{\theta} + t\mathbf{h} = (\boldsymbol{\alpha} + t\mathbf{a}, \beta + t\mathbf{b}, \int_0^\cdot (1 + t\eta) d\Lambda)$. Define the directional derivatives

$$\lim_{t \rightarrow 0} \frac{l_n^I(\boldsymbol{\theta} + t\mathbf{h}) - l_n^I(\boldsymbol{\theta})}{t} = S_n^\theta = S_{n,a}^\theta + S_{n,b}^\theta + S_{n,\eta}^\theta,$$

where

$$\begin{aligned}
S_{n,a}^{\boldsymbol{\theta}} &= \frac{1}{n} \sum_{i=1}^n \mathbf{a}^\top \mathbf{Z}_{1i} \left\{ \int_0^{\tau'} (1 - \phi_i^{\boldsymbol{\theta}}(u)) dN_i(u) - \int_0^{\tau'} Y_i(u) \phi_i^{\boldsymbol{\theta}}(u) (1 - \phi_i^{\boldsymbol{\theta}}(u)) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} d\Lambda(u) \right. \\
&\quad \left. + (N_i(\tau) - N_i(\tau')) (1 - \phi_i^{\boldsymbol{\theta}}(\tau')) - Y_i(\tau) \phi_i^{\boldsymbol{\theta}}(\tau') \right\} \\
S_{n,b}^{\boldsymbol{\theta}} &= \frac{1}{n} \sum_{i=1}^n \mathbf{b}^\top \mathbf{Z}_{2i} \left[\int_0^{\tau'} \left\{ 1 - (1 - \phi_i^{\boldsymbol{\theta}}(u)) \Lambda(u) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right\} dN_i(u) \right. \\
&\quad \left. + \int_0^{\tau'} Y_i(u) \phi_i^{\boldsymbol{\theta}}(u) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \left\{ (1 - \phi_i^{\boldsymbol{\theta}}(u)) \Lambda(u) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} - 1 \right\} d\Lambda(u) \right. \\
&\quad \left. - (N_i(\tau) - N_i(\tau')) (1 - \phi_i^{\boldsymbol{\theta}}(\tau')) \Lambda(\tau') e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} + Y_i(\tau) \phi_i^{\boldsymbol{\theta}}(\tau') \Lambda(\tau') e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right] \\
S_{n,\eta}^{\boldsymbol{\theta}} &= \frac{1}{n} \sum_{i=1}^n \int_0^{\tau'} \left[\eta(u) - \left\{ 1 - \phi_i^{\boldsymbol{\theta}}(u) \right\} e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \int_0^u \eta d\Lambda \right] dN_i(u) \\
&\quad + \int_0^{\tau'} Y_i(u) \phi_i^{\boldsymbol{\theta}}(u) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \left[\left\{ 1 - \phi_i^{\boldsymbol{\theta}}(u) \right\} e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \int_0^u \eta d\Lambda - \eta(u) \right] d\Lambda(u) \\
&\quad - (N_i(\tau) - N_i(\tau')) (1 - \phi_i^{\boldsymbol{\theta}}(\tau')) \int_0^{\tau'} \eta d\Lambda e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} + Y_i(\tau) \phi_i^{\boldsymbol{\theta}}(\tau') \int_0^{\tau'} \eta d\Lambda e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}}.
\end{aligned}$$

Their expectations are denoted as

$$S^{\boldsymbol{\theta}} = S_a^{\boldsymbol{\theta}} + S_b^{\boldsymbol{\theta}} + S_\eta^{\boldsymbol{\theta}} = E(S_{n,a}^{\boldsymbol{\theta}}) + E(S_{n,b}^{\boldsymbol{\theta}}) + E(S_{n,\eta}^{\boldsymbol{\theta}}).$$

Again let $\boldsymbol{\theta}_0$ be the true parameter and $\boldsymbol{\theta}$ another element in the parameter space.

Define $\Delta\boldsymbol{\theta} = \boldsymbol{\theta} - \boldsymbol{\theta}_0$ with

$$\Delta\boldsymbol{\alpha} = \boldsymbol{\alpha} - \boldsymbol{\alpha}_0, \Delta\boldsymbol{\beta} = \boldsymbol{\beta} - \boldsymbol{\beta}_0 \text{ and } \Delta\Lambda(\cdot) = \left\{ \Lambda(\cdot) - \Lambda_0(\cdot) \right\}.$$

Define $\text{lin}\Theta$ to be the linear space spanned by $\{\boldsymbol{\theta} - \boldsymbol{\theta}_0 : \boldsymbol{\theta} \text{ in parameter space}\}$. Let

$\boldsymbol{\theta}_t = \boldsymbol{\theta}_0 + t\Delta\boldsymbol{\theta}$. The functional Hessian is a linear operator $\text{lin}\Theta \mapsto l^\infty(H_p)$ defined as

$$\begin{aligned}
\dot{S}^{\boldsymbol{\theta}_0}(\Delta\boldsymbol{\theta})(\mathbf{h}) &= \lim_{t \rightarrow 0} \frac{S^{\boldsymbol{\theta}_t}(\mathbf{h}) - S^{\boldsymbol{\theta}_0}(\mathbf{h})}{t} \\
&= -\Delta\boldsymbol{\alpha}^\top \boldsymbol{\sigma}_a(\mathbf{h}) - \Delta\boldsymbol{\beta}^\top \boldsymbol{\sigma}_b(\mathbf{h}) - \int_0^{\tau'} \sigma_\eta(\mathbf{h})(u) d\Delta\Lambda(u) \quad (\text{A24})
\end{aligned}$$

with σ defined in (A22).

The following Lemma A2 is used in the proofs of Theorems 4 and 5. It tells us about the property of σ , the essential element in the functional Hessian.

Lemma A2. *Let the operator $\sigma : (\mathbf{a}, \mathbf{b}, \eta) \mapsto (\boldsymbol{\sigma}_a(\mathbf{h}), \boldsymbol{\sigma}_b(\mathbf{h}), \sigma_\eta(\mathbf{h}))$ be defined as in (A22). Under the conditions of Theorem 4, σ is a continuously invertible bijection from H_∞ to H_∞ .*

Proof of Lemma A2. First we prove that σ is injection by an identifiability argument.

Define an inner-product between $\sigma(\mathbf{h})$ and \mathbf{h} as

$$\begin{aligned} \langle \sigma(\mathbf{h}), \mathbf{h} \rangle &= \mathbf{a}^\top \boldsymbol{\sigma}_a(\mathbf{h}) + \mathbf{b}^\top \boldsymbol{\sigma}_b(\mathbf{h}) + \int_0^{\tau'} \sigma_\eta(\mathbf{h})(u) \eta(u) d\Lambda_0(u) \\ &= \int_0^{\tau'} E \left[\{K_1^{\boldsymbol{\theta}_0}(\mathbf{h})(u)\}^2 Y(u) \phi^{\boldsymbol{\theta}_0}(u) e^{\boldsymbol{\beta}_0^\top \mathbf{Z}_2} \right] d\Lambda_0(u) \\ &\quad + E \left[\{K_2^{\boldsymbol{\theta}_0}(\mathbf{h})\}^2 Y(\tau') \phi^{\boldsymbol{\theta}_0}(\tau') (1 - \phi^{\boldsymbol{\theta}_0}(\tau')) \right]. \end{aligned}$$

If $\langle \sigma(\mathbf{h}), \mathbf{h} \rangle = 0$, we have almost surely $K_2^{\boldsymbol{\theta}_0}(\mathbf{h}) = 0$ and $K_1^{\boldsymbol{\theta}_0}(\mathbf{h})(u) = 0$ a.e. $u \in [0, \tau']$.

Therefore,

$$\int_0^t K_1^{\boldsymbol{\theta}_0}(\mathbf{h})(u) \phi^{\boldsymbol{\theta}_0}(u) e^{\boldsymbol{\beta}_0^\top \mathbf{Z}_2} d\Lambda_0(u) = 0, \forall t \in [0, \tau'], a.s..$$

Calculating the integral, we have for any $t \in [0, \tau']$ a.s.

$$-\mathbf{a}^\top \mathbf{Z}_1 \phi^{\boldsymbol{\theta}_0}(t) + \mathbf{b}^\top \mathbf{Z}_2 \phi^{\boldsymbol{\theta}_0}(t) \Lambda_0(t) e^{\boldsymbol{\beta}_0^\top \mathbf{Z}_2} + \int_0^t \eta(u) d\Lambda_0(u) \phi^{\boldsymbol{\theta}_0}(t) e^{\boldsymbol{\beta}_0^\top \mathbf{Z}_2} = 0.$$

Setting $t = 0$, we have $-\mathbf{a}^\top \mathbf{Z}_1 \phi^{\boldsymbol{\theta}_0}(0) = 0$, so $\mathbf{a}^\top \mathbf{Z}_1 = 0$. By Assumption 2, $\mathbf{a} = 0$.

Plugging $\mathbf{a} = 0$ into $K_2^{\boldsymbol{\theta}_0}$ yields

$$K_2^{\boldsymbol{\theta}_0}(\mathbf{h}) = e^{\boldsymbol{\beta}_0^\top \mathbf{Z}_2} \left\{ \mathbf{b}^\top \mathbf{Z}_2 \Lambda_0(\tau') - \int_0^{\tau'} \eta(u) d\Lambda_0(u) \right\} = 0, a.s..$$

Again, $\mathbf{b}^\top \mathbf{Z}_2 = \int_0^{\tau'} \eta(u) d\Lambda_0(u) / \Lambda_0(\tau')$ is deterministic, so $\mathbf{b} = 0$. This way η must also be constantly zero. As a result, $\sigma(\mathbf{h}) = \sigma(\mathbf{h}') \Rightarrow (\sigma(\mathbf{h} - \mathbf{h}'), \mathbf{h} - \mathbf{h}') = 0 \Rightarrow \mathbf{h} = \mathbf{h}'$.

To show it is a bijection, we apply Theorem 3.11 in Conway (1990). It suffices to decompose σ as the sum of one invertible operator and one compact operator. The invertible operator is defined as

$$\Sigma(\mathbf{h}) = \left(E \left(\mathbf{Z}_1 \mathbf{Z}_1^\top \right) \mathbf{a}, E \left(\mathbf{Z}_2 \mathbf{Z}_2^\top \right) \mathbf{b}, \eta(t) E \left\{ e^{\boldsymbol{\beta}_0^\top \mathbf{Z}_2} \phi^{\boldsymbol{\theta}_0}(t) Y(t) \right\} \right).$$

Since $E(\mathbf{Z}_1 \mathbf{Z}_1^\top)$, $E(\mathbf{Z}_2 \mathbf{Z}_2^\top)$ are both positive definite, and $\inf_{t \in [0, \tau']} E e^{\beta_0^\top \mathbf{Z}_2} \phi^{\theta_0}(t) Y(t) > 0$, the inverse exists as

$$\Sigma^{-1}(\mathbf{h}) = \left(\left[E\{\mathbf{Z}_1 \mathbf{Z}_1^\top\} \right]^{-1} \mathbf{a}, \left[E\{\mathbf{Z}_2 \mathbf{Z}_2^\top\} \right]^{-1} \mathbf{b}, \eta(t) \left[E\{e^{\beta_0^\top \mathbf{Z}_2} \phi^{\theta_0}(t) Y(t)\} \right]^{-1} \right).$$

For the compactness of $\sigma(\mathbf{h}) - \Sigma(\mathbf{h})$, classical Helly-selection plus dominated convergence method applies as all terms are conveniently bounded. \square

The proof of Theorem 4 is the application of Theorem 3.3.1 from Van der Vaart and Wellner (1996). We shall verify all the required conditions for the Theorem.

Proof of Theorem 4. Since we work under a modified Assumption 3' now, the martingale representation in (10) needs to change accordingly beyond τ' . We still use $M_i(t)$ as the notation. Define the filtrations $\{\mathcal{F}_t : t \in [0, \tau]\}$. On $[0, \tau']$, \mathcal{F}_t is the natural σ -algebra generated by $\{N_i(t), Y_i(t), \mathbf{Z}_{1i}, \mathbf{Z}_{2i}, i = 1, \dots, n\}$. Since there is no extra information in the tail window (τ', τ) , we set $\mathcal{F}_t = \mathcal{F}_{\tau'}$ for $t \in (\tau', \tau)$. \mathcal{F}_τ is the σ -algebra generated by $\{N_i(\tau) - N_i(\tau'), Y_i(\tau), \mathbf{Z}_{1i}, \mathbf{Z}_{2i}, i = 1, \dots, n\}$, where $Y_i(\tau) = Y_i(\tau') - dN_i(\tau')$ is measurable in $\mathcal{F}_{\tau'}$. The filtrations on $[0, \tau']$ stay the same, so $M_i(t)$ defined in (10) is still a martingale up to time τ' . In the tail window (τ', τ) , we set $M_i(t)$ constantly equals $M_i(\tau')$. To extend its definition to time τ , we define

$$dM_i(\tau) = M_i(\tau) - M_i(\tau') = \{N_i(\tau) - N_i(\tau')\} - Y_i(\tau) \phi_i^{\theta_0}(\tau'). \quad (\text{A25})$$

It is easy to verify that $E[M_i(\tau) | \mathcal{F}_{\tau'}] = M_i(\tau')$, so $M_i(t)$ thus defined is a martingale with respect to the new filtrations $\{\mathcal{F}_t : t \in [0, \tau'] \cup \{\tau\}\}$. Analogously, we define the process $M_i^\theta(\cdot)$ which replaces the true parameter θ_0 in $M_i(\cdot)$ by arbitrary θ in the parameter space. Apparently, $M_i^{\theta_0}(\cdot) = M_i(\cdot)$. From here, we establish the needed results based on the martingale theory.

First, we prove weak convergence of the empirical score

$$\sqrt{n}(S_n^{\theta_0} - S^{\theta_0}) \xrightarrow{l^\infty(H^p)} \mathcal{W}. \quad (\text{A26})$$

Notice that $S_1^{\theta_0} - S^{\theta_0}$ is a martingale integral with respect to (A25). The weak convergence follows from martingale central limit theorem. The covariance process is given by the expectation of its quadratic variation:

$$\begin{aligned} \text{Cov}(\mathcal{G}(\mathbf{h}), \mathcal{G}(\mathbf{h}^*)) &= E \left[\int_0^{\tau'} K_1^{\theta_0}(\mathbf{h}) K_1^{\theta_0}(\mathbf{h}^*) Y(u) \phi_0(u) e^{\beta_0^\top \mathbf{Z}_2} d\Lambda_0(u) \right. \\ &\quad \left. + K_2^{\theta_0}(\mathbf{h}) K_2^{\theta_0}(\mathbf{h}^*) \phi_0(\tau') \{1 - \phi_0(\tau')\} \right], \end{aligned}$$

where K_1 and K_2 are defined as in (A23).

Next, we verify the approximation condition

$$\sqrt{n} \left(S_n^{\hat{\theta}} - S^{\hat{\theta}} - S_n^{\theta_0} - S^{\theta_0} \right) = o_p(1). \quad (\text{A27})$$

Consider the class $\{S_1^{\theta}(\mathbf{h}) - S_1^{\theta_0}(\mathbf{h}) : \|\theta - \theta_0\| \leq \varepsilon, \mathbf{h} \in H_p\}$. All terms involved in this class are uniformly bounded with uniformly bounded variation, so it is a Donsker class for the set of observable random variables. By checking that ϕ_i^{θ} is Lipschitz in θ under the $l^\infty(H_p)$ norm, we have almost surely

$$\sup_{t, \mathbf{Z}_2, \mathbf{Z}_1} |\phi_i^{\theta}(t) - \phi_i^{\theta_0}(t)| = O(\|\theta - \theta_0\|),$$

and similarly

$$\sup_{t, \mathbf{Z}_2, \mathbf{Z}_1} |\phi_i^{\theta}(t) \Lambda(t) - \phi_i^{\theta_0}(t) \Lambda_0(t)| = O(\|\theta - \theta_0\|).$$

For a single summand in the score,

$$\sup_{h \in H_p} E[S_1^{\theta}(\mathbf{h}) - S_1^{\theta_0}(\mathbf{h})]^2 = O(\|\theta - \theta_0\|^2).$$

We plug $\hat{\theta}$ into the expression above. Thus, the variance of the limiting process of (A27) is $o(1)$ by the consistency of $\hat{\theta}$ from Theorem 3', so the process itself is $o_p(1)$.

We then show the Fréchet differentiability of expected score S at θ_0 in the direction of $\hat{\theta} - \theta_0$,

$$S^{\hat{\theta}_t} - S^{\theta_0} = t \dot{S}^{\theta_0}(\hat{\theta} - \theta_0) + o_p(t\|\hat{\theta} - \theta_0\|). \quad (\text{A28})$$

We use a shorthand notation for the expected score at θ :

$$S^{\theta}(\mathbf{h}) = E \left[\int_0^{\tau'} K_1^{\theta}(\mathbf{h})(u) dM^{\theta}(u) + K_2^{\theta}(\mathbf{h}) dM^{\theta}(\tau) \right] = E \left[\int_0^{\tau} V^{\theta}(\mathbf{h})(u) dM^{\theta}(u) \right],$$

by setting

$$V^{\boldsymbol{\theta}}(\mathbf{h})(t) = I(t \leq \tau')K_1^{\boldsymbol{\theta}}(\mathbf{h})(t) + I(t = \tau)K_2^{\boldsymbol{\theta}}(\mathbf{h}).$$

By the Lipschitz continuity with respect to $\|\boldsymbol{\theta}\|$ for all terms involved, $K_1^{\boldsymbol{\theta}}(\mathbf{h})$, $K_2^{\boldsymbol{\theta}}(\mathbf{h})$ and $dM^{\boldsymbol{\theta}}$,

$$\begin{aligned} & S^{\boldsymbol{\theta}_t}(\mathbf{h}) - S^{\boldsymbol{\theta}}(\mathbf{h}) \\ = & E \left[\int_0^{\tau'} V^{\boldsymbol{\theta}_t}(\mathbf{h})(u) dM^{\boldsymbol{\theta}_t}(u) \right] \\ = & E \left[\int_0^{\tau'} V^{\boldsymbol{\theta}_0}(\mathbf{h})(u) d\{M^{\boldsymbol{\theta}_t}(u) - M^{\boldsymbol{\theta}_0}(u)\} \right] + E \left[\int_0^{\tau'} V^{\boldsymbol{\theta}_t}(\mathbf{h})(u) dM^{\boldsymbol{\theta}_0}(u) \right] \\ & + E \left[\int_0^{\tau'} \{V^{\boldsymbol{\theta}_t}(\mathbf{h})(u) - V^{\boldsymbol{\theta}_0}(\mathbf{h})(u)\} d\{M^{\boldsymbol{\theta}_t}(u) - M^{\boldsymbol{\theta}_0}(u)\} \right] \\ = & t\dot{S}^{\boldsymbol{\theta}_0}(\boldsymbol{\theta} - \boldsymbol{\theta}_0)(\mathbf{h}) + 0 + O_p(t^2\|\boldsymbol{\theta} - \boldsymbol{\theta}_0\|^2). \end{aligned}$$

Again, we plug-in $\hat{\boldsymbol{\theta}}$ and use the consistency result to verify the condition (A28).

Afterwards, we find the local inverse of the functional Hessian in (A24). We have shown in Lemma A2 that the functional operator σ is a continuously invertible bijection from H_∞ to H_∞ . The invertibility of $\dot{S}^{\boldsymbol{\theta}_0}$ in H_p follows from the following argument. By the continuous invertibility of σ , there is some q so that $\sigma^{-1}(H_q) \subseteq H_p$, and

$$\begin{aligned} & \inf_{\Delta\boldsymbol{\theta} \in \text{lin}\Theta} \frac{\sup_{\mathbf{h} \in H_p} |(\boldsymbol{\alpha} - \boldsymbol{\alpha}_0)^\top \boldsymbol{\sigma}_a(\mathbf{h}) + (\boldsymbol{\beta} - \boldsymbol{\beta}_0)^\top \boldsymbol{\sigma}_b(\mathbf{h}) + \int_0^{\tau'} \sigma_\eta(\mathbf{h}) d(\Lambda - \Lambda_0)|}{\|\Delta\boldsymbol{\theta}\|_{l^\infty(H_p)}} \\ \geq & \inf_{\Delta\boldsymbol{\theta} \in \text{lin}\Theta} \frac{\sup_{\mathbf{h} \in \sigma^{-1}(H_q)} |(\boldsymbol{\alpha} - \boldsymbol{\alpha}_0)^\top \boldsymbol{\sigma}_a(\mathbf{h}) + (\boldsymbol{\beta} - \boldsymbol{\beta}_0)^\top \boldsymbol{\sigma}_b(\mathbf{h}) + \int_0^{\tau'} \sigma_\eta(\mathbf{h}) d(\Lambda - \Lambda_0)|}{p\|\Delta\boldsymbol{\theta}\|} \\ = & \inf_{\Delta\boldsymbol{\theta} \in \text{lin}\Theta} \frac{\sup_{\mathbf{h} \in H_q} |\Delta\boldsymbol{\theta}(\mathbf{h})|}{p\|\Delta\boldsymbol{\theta}\|} > \frac{q}{2p}. \end{aligned} \tag{A29}$$

Finally, let us put everything together. The NPMLE $\hat{\boldsymbol{\theta}}$ is shown to be consistent in Theorem 3', and (A26), (A27), (A28) and (A29) verify the conditions of Theorem 3.3.1 from Van der Vaart and Wellner (1996). \square

Proof of Theorem 5. The proof for the continuous invertibility of $\hat{\sigma}$ is similar to the proof of Lemma A2. The approximation error between the natural estimator $\hat{\sigma}$ and

Louis' formula variance estimator using (9) again comes from the “ghost copies” like the case in Lemma 1, so the same argument applies to show their asymptotic equivalence.

□

B Appendix B: Variance Estimator

B.1 Derivatives of Log-likelihood

Let $l^c(\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\lambda}) = \sum_{i=1}^n l_i^c(\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\lambda})$ be the complete data log-likelihood,

$$\begin{aligned} l_i^c(\boldsymbol{\alpha}, \boldsymbol{\beta}, \boldsymbol{\lambda}) = & (A_i + M_i)\boldsymbol{\alpha}^\top \mathbf{Z}_{1i} - (1 + M_i)\log(1 + e^{\boldsymbol{\alpha}^\top \mathbf{Z}_{1i}}) \\ & + \delta_i^1 A_i \sum_{k=1}^K I\{X_i = t_k\}(\log \lambda_k + \boldsymbol{\beta}^\top \mathbf{Z}_{2i}) - A_i \sum_{k:t_k \leq X_i} \lambda_k e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \\ & + M_i \sum_{k:t_k < Q_i} I\{\kappa_i = k\} \left(\log \lambda_k + \boldsymbol{\beta}^\top \mathbf{Z}_{2i} - \sum_{h=1}^k \lambda_h e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right). \end{aligned}$$

Its gradient is given by

$$\nabla l_i^c = \left(\frac{\partial l_i^c}{\partial \boldsymbol{\alpha}}, \frac{\partial l_i^c}{\partial \boldsymbol{\beta}}, \frac{\partial l_i^c}{\partial \boldsymbol{\lambda}} \right)^\top,$$

where

$$\begin{aligned} \frac{\partial l_i^c}{\partial \boldsymbol{\alpha}} = & \mathbf{Z}_{1i} \left\{ A_i + M_i - (1 + M_i) \frac{e^{\boldsymbol{\alpha}^\top \mathbf{Z}_{1i}}}{1 + e^{\boldsymbol{\alpha}^\top \mathbf{Z}_{1i}}} \right\} = \mathbf{Z}_{1i} \{A_i - p_i + M_i(1 - p_i)\}, \\ \frac{\partial l_i^c}{\partial \boldsymbol{\beta}} = & \mathbf{Z}_{2i} \left\{ A_i \delta_i^1 + M_i - \left(A_i \sum_{k:t_k \leq X_i} \lambda_k + M_i \sum_{k=1}^{\kappa_i} \lambda_k \right) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right\} \\ = & \mathbf{Z}_{2i} \left\{ A_i \delta_i^1 + M_i - A_i \Lambda_i(X_i) - M_i \Lambda_i(\kappa_i) \right\}, \\ \frac{\partial l_i^c}{\partial \lambda_k} = & \left(A_i \delta_i^1 I\{X_i = t_k\} + M_i I\{\kappa_i = k\} \right) \frac{1}{\lambda_k} - \left(A_i I\{t_k \leq X_i\} + M_i I\{\kappa_i \geq t_k\} \right) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \\ = & A_i \left(\frac{\delta_i^1 I\{X_i = t_k\}}{\lambda_k} - I\{t_k \leq X_i\} e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right) + M_i \left(\frac{I\{\kappa_i = k\}}{\lambda_k} - I\{\kappa_i \geq t_k\} e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right). \end{aligned}$$

Its Hessian is given by

$$\nabla^2 l_i^c = \begin{pmatrix} \frac{\partial^2 l_i^c}{\partial \boldsymbol{\alpha} \partial \boldsymbol{\alpha}^\top} & 0 & 0 \\ 0 & \frac{\partial^2 l_i^c}{\partial \boldsymbol{\beta} \partial \boldsymbol{\beta}^\top} & \frac{\partial^2 l_i^c}{\partial \boldsymbol{\beta} \partial \boldsymbol{\lambda}^\top} \\ 0 & \left[\frac{\partial^2 l_i^c}{\partial \boldsymbol{\beta} \partial \boldsymbol{\lambda}^\top} \right]^\top & \text{diag} \left(\frac{\partial^2 l_i^c}{\partial \lambda_k^2} \right) \end{pmatrix},$$

where

$$\begin{aligned}
\frac{\partial^2 l_i^c}{\partial \boldsymbol{\alpha} \partial \boldsymbol{\alpha}^\top} &= \mathbf{Z}_{1i} \mathbf{Z}_{1i}^\top \left\{ - (1 + M_i) \frac{e^{\boldsymbol{\alpha}^\top \mathbf{Z}_{1i}}}{(1 + e^{\boldsymbol{\alpha}^\top \mathbf{Z}_{1i}})^2} \right\} = - \mathbf{Z}_{1i} \mathbf{Z}_{1i}^\top (1 + M_i) p_i (1 - p_i), \\
\frac{\partial^2 l_i^c}{\partial \boldsymbol{\beta} \partial \boldsymbol{\beta}^\top} &= \mathbf{Z}_{2i} \mathbf{Z}_{2i}^\top \left\{ - \left(A_i \sum_{k: t_k \leq X_i} \lambda_k + M_i \sum_{k=1}^{\kappa_i} \lambda_k \right) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right\}, \\
\frac{\partial^2 l_i^c}{\partial \boldsymbol{\beta} \partial \lambda_k} &= \mathbf{Z}_{2i} \left\{ - \left(A_i I\{t_k \leq X_i\} + M_i I\{t_k \leq \kappa_i\} \right) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right\}, \\
\frac{\partial^2 l_i^c}{\partial \lambda_k^2} &= - \left(A_i \delta_i^1 I\{X_i = t_k\} + M_i I\{\kappa_i = k\} \right) \frac{1}{\lambda_k^2}, \\
\frac{\partial^2 l_i^c}{\partial \boldsymbol{\alpha} \partial \boldsymbol{\beta}^\top} &= \frac{\partial^2 l_i^c}{\partial \boldsymbol{\alpha} \partial \boldsymbol{\lambda}^\top} = \frac{\partial^2 l_i^c}{\partial \lambda_k \partial \lambda_h} = 0, \quad k \neq h.
\end{aligned}$$

B.2 Conditional Expectations

By the conditional expectations (5) - (7), we are able to calculate the ‘first order’ conditional expectations, $E[\nabla l_i^c | \mathcal{O}]$ and $E[\nabla^2 l_i^c | \mathcal{O}]$:

$$\begin{aligned}
E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\alpha}} \right] &= \mathbf{Z}_{1i} \left\{ E(A_i) - p_i + E(M_i)(1 - p_i) \right\}, \\
E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\beta}} \right] &= \mathbf{Z}_{2i} \left[E(A_i) \left\{ \delta_i^1 + \log S_i(X_i) \right\} + E(M_i) \left\{ 1 + \sum_{k: t_k < Q_j} P(\tilde{T}_{ij} = t_k) \log S_i(t_k) \right\} \right], \\
E \left[\frac{\partial l_i^c}{\partial \lambda_k} \right] &= E(A_i) \left\{ \frac{\delta_i^1 I\{t_k = X_i\}}{\lambda_k} - I\{t_k \leq X_i\} e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right\} + E(M_i) \left\{ \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k} - P(\tilde{T}_{ij} \geq t_k) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right\}. \\
\\
E \left[\frac{\partial^2 l_i^c}{\partial \boldsymbol{\alpha} \partial \boldsymbol{\alpha}^\top} \right] &= - \mathbf{Z}_{1i} \mathbf{Z}_{1i}^\top (1 + E(M_i)) p_i (1 - p_i), \\
E \left[\frac{\partial^2 l_i^c}{\partial \boldsymbol{\beta} \partial \boldsymbol{\beta}^\top} \right] &= \mathbf{Z}_{2i} \mathbf{Z}_{2i}^\top \left\{ E(A_i) \log S_i(X_i) + E(M_i) \sum_{k: t_k < Q_i} P(\tilde{T}_{ij} = t_k) \log S_i(t_k) \right\}, \\
E \left[\frac{\partial^2 l_i^c}{\partial \boldsymbol{\beta} \partial \lambda_k} \right] &= - \mathbf{Z}_{2i} \left\{ E(A_i) I\{t_k \leq X_i\} + E(M_i) P(t_k \leq \kappa_i) \right\} e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}}, \\
E \left[\frac{\partial^2 l_i^c}{\partial \lambda_k^2} \right] &= - \left\{ E(A_i) \delta_i^1 I\{\tilde{T}_{ij} = t_k\} + E(M_i) P(\tilde{T}_{ij} = t_k) \right\} \frac{1}{\lambda_k^2}.
\end{aligned}$$

To calculate ‘second order’ expectation $E[\nabla l_i^c \nabla l_i^{c\top} | \mathcal{O}]$, we first compute the conditional variances:

$$\begin{aligned}\text{Var}[A_i | \mathcal{O}] &= \delta_i^c \frac{p_i(1-p_i)S_i(X_i)}{\{1-p_i+p_iS_i(X_i)\}^2}, \\ \text{Var}[M_i | \mathcal{O}] &= \frac{p_i[1-S_i(Q_i)]}{\{1-p_i+p_iS_i(Q_i)\}^2}.\end{aligned}$$

Then,

$$\begin{aligned}
E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\alpha}} \frac{\partial l_i^c}{\partial \boldsymbol{\alpha}}^\top \right] &= E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\alpha}} \right] E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\alpha}} \right]^\top + \mathbf{Z}_{1i} \mathbf{Z}_{1i}^\top \{ (1 - p_i)^2 \text{Var}(M_i) + \text{Var}(A_i) \}, \\
E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\alpha}} \frac{\partial l_i^c}{\partial \boldsymbol{\beta}}^\top \right] &= E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\alpha}} \right] E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\beta}} \right]^\top + \mathbf{Z}_{1i} \mathbf{Z}_{2i}^\top \left[\text{Var}(A_i) \{ \delta_i^1 + \log S_i(X_i) \} \right. \\
&\quad \left. + \text{Var}(M_i) (1 - p_i) \left\{ 1 + \sum_{k: t_k < Q_i} P(\tilde{T}_{ij} = t_k) \log S_i(t_k) \right\} \right], \\
E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\beta}} \frac{\partial l_i^c}{\partial \boldsymbol{\beta}}^\top \right] &= E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\beta}} \right] E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\beta}} \right]^\top + \mathbf{Z}_{2i} \mathbf{Z}_{2i}^\top \left[\text{Var}(A_i) \{ \delta_i^1 + \log S_i(X_i) \}^2 \right. \\
&\quad \left. + \text{Var}(M_i) \left\{ 1 + \sum_{k: t_k < Q_i} P(\tilde{T}_{ij} = t_k) \log S_i(t_k) \right\}^2 \right. \\
&\quad \left. + E(M_i) \left\{ \sum_{k: t_k < Q_i} P(\tilde{T}_{ij} = t_k) \log S_i(t_k)^2 - \left(\sum_{k: t_k < Q_i} P(\tilde{T}_{ij} = t_k) \log S_i(t_k) \right)^2 \right\} \right], \\
E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\alpha}} \frac{\partial l_i^c}{\partial \lambda_k} \right] &= E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\alpha}} \right] E \left[\frac{\partial l_i^c}{\partial \lambda_k} \right] + \mathbf{Z}_{1i} \left[\text{Var}(A_i) \left\{ \frac{\delta_i^1 I\{t_k = X_i\}}{\lambda_k} - I\{t_k \leq X_i\} e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right\} \right. \\
&\quad \left. + \text{Var}(M_i) (1 - p_i) \left\{ \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k} - P(\tilde{T}_{ij} \geq t_k) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right\} \right], \\
E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\beta}} \frac{\partial l_i^c}{\partial \lambda_k} \right] &= E \left[\frac{\partial l_i^c}{\partial \boldsymbol{\beta}} \right] E \left[\frac{\partial l_i^c}{\partial \lambda_k} \right] \\
&\quad + \mathbf{Z}_{2i} \left[\text{Var}(A_i) \{ \delta_i^1 + \log S_i(X_i) \} \left\{ \frac{\delta_i^1 I\{t_k = X_i\}}{\lambda_k} - I\{t_k \leq X_i\} e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right\} \right. \\
&\quad + \text{Var}(M_i) \left\{ \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k} - P(\tilde{T}_{ij} \geq t_k) e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \right\} \left\{ 1 + \sum_{h: t_h < Q_i} P(\tilde{T}_{ij} = t_h) \log S_i(t_h) \right\} \\
&\quad - E(M_i) \left\{ \sum_{h: t_h < Q_i} P(\tilde{T}_{ij} = t_h) \log S_i(t_h) \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k} - \frac{P(\tilde{T}_{ij} = t_k) \log S_i(t_k)}{\lambda_k} \right. \\
&\quad \left. - P\{\tilde{T}_{ij} \geq t_k\} e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \sum_{h: t_h < Q_i} P(\tilde{T}_{ij} = t_h) \log S_i(t_h) \right. \\
&\quad \left. \left. + e^{\boldsymbol{\beta}^\top \mathbf{Z}_{2i}} \sum_{h=k}^{t_h < Q_i} P(\tilde{T}_{ij} = t_h) \log S_i(t_h) \right\} \right],
\end{aligned}$$

$$\begin{aligned}
E \left[\frac{\partial l_i^c}{\partial \lambda_k} \frac{\partial l_i^c}{\partial \lambda_h} \right] &= E A_i \left\{ -\frac{\delta_i^1 I\{X_i = t_{k \vee h}\}}{\lambda_{k \vee h}} e^{\beta^\top \mathbf{Z}_{2i}} + I\{X_i \geq t_{k \vee h}\} e^{2\beta^\top \mathbf{Z}_{2i}} \right\} \\
&+ E(A_i) E(M_i) \left\{ \frac{\delta_i^1 I\{\tilde{T}_{ij} = t_k\}}{\lambda_k} - I\{X_i \geq t_k\} e^{\beta^\top \mathbf{Z}_{2i}} \right\} \left\{ \frac{P(\tilde{T}_{ij} = t_h)}{\lambda_h} - P(\tilde{T}_{ij} \geq t_h) e^{\beta^\top \mathbf{Z}_{2i}} \right\} \\
&+ E(A_i) E(M_i) \left\{ \frac{\delta_i^1 I\{X_i = t_h\}}{\lambda_h} - I\{X_i \geq t_h\} e^{\beta^\top \mathbf{Z}_{2i}} \right\} \left\{ \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k} - P(\tilde{T}_{ij} \geq t_k) e^{\beta^\top \mathbf{Z}_{2i}} \right\} \\
&+ E[M_i^2 - M_i] \left\{ \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k} - P(\tilde{T}_{ij} \geq t_k) e^{\beta^\top \mathbf{Z}_{2i}} \right\} \left\{ \frac{P(\tilde{T}_{ij} = t_h)}{\lambda_h} - P(\tilde{T}_{ij} \geq t_h) e^{\beta^\top \mathbf{Z}_{2i}} \right\} \\
&+ E(M_i) \left\{ -\frac{P(\tilde{T}_{ij} = t_{k \vee h})}{\lambda_{k \vee h}} e^{\beta^\top \mathbf{Z}_{2i}} + P(\kappa_i \geq t_{k \vee h}) e^{2\beta^\top \mathbf{Z}_{2i}} \right\}, \\
E \left[\frac{\partial l_i^c}{\partial \lambda_k} \frac{\partial l_i^c}{\partial \lambda_k} \right] &= E A_i \left\{ \frac{\delta_i^1 I\{\tilde{T}_{ij} = t_k\}}{\lambda_k} - I\{X_i \geq t_k\} e^{\beta^\top \mathbf{Z}_{2i}} \right\}^2 \\
&+ E(A_i) E(M_i) \left\{ \frac{\delta_i^1 I\{\tilde{T}_{ij} = t_k\}}{\lambda_k} - I\{X_i \geq t_k\} e^{\beta^\top \mathbf{Z}_{2i}} \right\} \left\{ \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k} - P(\tilde{T}_{ij} \geq t_k) e^{\beta^\top \mathbf{Z}_{2i}} \right\} \\
&+ E(A_i) E(M_i) \left\{ \frac{\delta_i^1 I\{\tilde{T}_{ij} = t_k\}}{\lambda_k} - I\{X_i \geq t_k\} e^{\beta^\top \mathbf{Z}_{2i}} \right\} \left\{ \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k} - P(\tilde{T}_{ij} \geq t_k) e^{\beta^\top \mathbf{Z}_{2i}} \right\} \\
&+ E[M_i^2 - M_i] \left\{ \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k} - P(\tilde{T}_{ij} \geq t_k) e^{\beta^\top \mathbf{Z}_{2i}} \right\} \left\{ \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k} - P(\tilde{T}_{ij} \geq t_k) e^{\beta^\top \mathbf{Z}_{2i}} \right\} \\
&+ E(M_i) \left\{ \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k^2} - 2 \frac{P(\tilde{T}_{ij} = t_k)}{\lambda_k} e^{\beta^\top \mathbf{Z}_{2i}} + P(\tilde{T}_{ij} \geq t_k) e^{2\beta^\top \mathbf{Z}_{2i}} \right\}.
\end{aligned}$$

Figure 1: Study entry times for all individuals in the SAB data (left), and left truncated Kaplan-Meier curves (95% confidence intervals) for the SAB events (right).

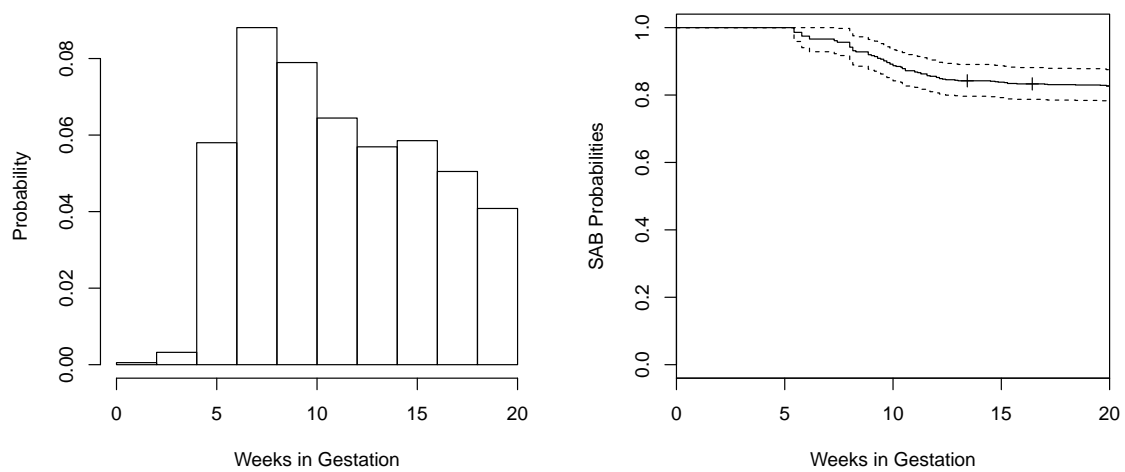


Table 1: Simulation results using the EM algorithm for NPMLE.

		$n = 200$				$n = 1000$			
	True Value	Estimate	Sample SD	SE	Coverage	Estimate	Sample SD	SE	Coverage
10% Truncation, 0% Censoring									
α_0	1.00	1.01	0.79	0.75	94.0 %	0.98	0.35	0.33	93.6 %
α_1	-0.63	-0.64	0.20	0.19	94.8 %	-0.63	0.09	0.08	94.3 %
α_2	1.00	1.00	0.36	0.37	95.6 %	1.01	0.16	0.16	94.8 %
β_1	-0.20	-0.23	0.20	0.17	92.2 %	-0.20	0.07	0.07	95.6 %
β_2	0.30	0.33	0.34	0.32	94.2 %	0.29	0.14	0.13	93.4 %
20% Truncation, 0% Censoring									
α_0	1.00	0.97	0.80	0.79	94.8 %	0.99	0.34	0.35	96.0 %
α_1	-0.63	-0.64	0.21	0.20	95.4 %	-0.63	0.09	0.09	96.2 %
α_2	1.00	0.98	0.40	0.39	95.4 %	0.99	0.17	0.17	95.2 %
β_1	-0.20	-0.20	0.20	0.18	94.6 %	-0.20	0.07	0.07	95.2 %
β_2	0.30	0.31	0.37	0.34	94.6 %	0.30	0.14	0.14	94.2 %
10% Truncation, 20% Censoring									
α_0	1.00	1.18	0.97	0.99	96.6 %	1.02	0.41	0.42	95.8 %
α_1	-0.63	-0.69	0.25	0.26	96.2 %	-0.64	0.11	0.11	96.2 %
α_2	1.00	1.01	0.50	0.49	95.4 %	1.00	0.20	0.21	96.0 %
β_1	-0.20	-0.21	0.30	0.26	91.6 %	-0.21	0.11	0.11	94.4 %
β_2	0.30	0.31	0.53	0.49	93.4 %	0.30	0.21	0.20	93.8 %
20% Truncation, 20% Censoring									
α_0	1.00	1.05	1.00	0.96	95.8 %	0.98	0.37	0.41	97.0 %
α_1	-0.63	-0.66	0.27	0.25	96.6 %	-0.63	0.10	0.11	96.6 %
α_2	1.00	1.05	0.49	0.47	95.6 %	1.01	0.20	0.20	94.6 %
β_1	-0.20	-0.19	0.30	0.26	90.4 %	-0.20	0.11	0.11	95.0 %
β_2	0.30	0.33	0.54	0.48	92.2 %	0.31	0.21	0.20	94.8 %

Table 2: Cure rate model versus naive model fits for SAB data

	Cure model		Separate models	
	Estimate (SE)	P-value	Estimate (SE)	P-value
Logistic				
Intercept	-0.74 (0.54)	0.17	-2.25 (0.49)	<0.01
Healthy	-0.54 (0.49)	0.27	-0.92 (0.45)	0.04
Diseased Control	0.18 (0.31)	0.56	0.01 (0.28)	0.98
BMI	-0.37 (0.18)	0.04	-0.11 (0.16)	0.51
Gravidity>1	0.01 (0.3)	0.97	0.2 (0.27)	0.46
Smoking	0.41 (0.37)	0.27	0.65 (0.34)	0.06
Alcohol	-0.1 (0.29)	0.73	-0.24 (0.26)	0.35
Cox PH				
Healthy Control	-0.36 (0.38)	0.34	-0.41 (0.5)	0.42
Diseased Control	-0.34 (0.25)	0.17	-0.29 (0.32)	0.36
BMI	-0.35 (0.09)	<0.01	-0.84 (0.22)	<0.01
Gravidity>1	-0.52 (0.23)	0.02	-0.38 (0.28)	0.18
Smoking	-1.01 (0.33)	<0.01	-0.65 (0.36)	0.08
Alcohol	0.66 (0.26)	0.01	0.87 (0.29)	<0.01

Figure 2: Left truncated Kaplan-Meier curves for SAB events according to BMI (top) or alcohol (bottom), among the full data set (left) and without the observed cured individuals (right); the p -values are from the cure model (Table 2).

